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Lewis A. Conner.....**Editor**

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Symposium on the Thyroid Heart

Vol. VIII OCTOBER, 1932 No. 1

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CONTENTS FOR OCTOBER, 1932

Symposium on the Thyroid Heart

The Mechanism of Adjustment of the Circulation in Hyperthyroidism (Thyrotoxicosis). Wallace M. Yater, M.D., Washington, D. C. 1

Cardiac Histopathology in Thyroid Disease. Preliminary Report. Carl V. Weller, M.D., R. C. Wanstrom, M.D., Harold Gordon, M.D., and John C. Bugher, M.D., Ann Arbor, Mich. 8

A Study of the Heart in Hyperthyroidism. Geoffrey Rake, M.B., and Donald McEachern, M.D., Baltimore, Md. 19

The Heart Rate During Sleep in Graves' Disease and in Neurogenic Sinus Tachycardia. Ernst P. Boas, M.D., New York, N. Y. 24

The Signs and Symptoms of Heart Changes in Toxic Goiter. Clough Turrill Burnett, M.D., and Edgar Durbin, M.D., Denver, Colo. 29

A Clinical Study of Goiter in the Pacific Northwest, With Special Reference to the State of the Heart. Noble W. Jones, M.D., Dean B. Seabrook, M.D., and Frank R. Menne, M.D., Portland, Ore. 41

Cardiovascular Symptomatology in Exophthalmic Goiter. J. Lerman, M.D., and J. H. Means, M.D., Boston, Mass. 55

The Heart in Hyperthyroidism. A Clinical and Experimental Study. E. Cowles Andrus, M.D., Baltimore, Md. 66

The Heart in Hyperthyroidism—an Experimental Study. Frank R. Menne, M.D., Roger H. Keane, A.B., Robert T. Henry, A.B., and Noble W. Jones, M.D., Portland, Ore. 75

Cardiac Status After Prolonged Thyrotoxicosis. J. Marion Read, M.D., San Francisco, Calif. 84

Myxedema Heart. A Report Based Upon a Study of 17 Cases of Myxedema. George Fahr, M.D., Minneapolis, Minn. 91

Congestive Heart Failure and Hypertrophy in Hyperthyroidism: A Clinical and Pathological Study of 178 Fatal Cases. Edwin J. Kepler, M.D., and Arlie R. Barnes, M.D., Rochester, Minn. 102

Studies in Thyroid Heart Disease. Angina Pectoris and Hyperthyroidism. Morris W. Lev, M.D., and Walter W. Hamburger, M.D., Chicago, Ill. 100

The Influence of Thyroid Extract and Hyperthyroidism on the Electrocardiogram, With Special Reference to the T-Waves. Johnson McGuire, M.D., and Margaret Foulger, M.D., Cincinnati, Ohio 114

Auricular Fibrillation in Graves' Disease. Paul S. Barker, M.D., Ann Arbor, Mich., Anne L. Bohning, M.D., Chicago, Ill., and Frank N. Wilson, M.D., Ann Arbor, Mich. 121

The Incidence of Auricular Fibrillation and Results of Quinidine Therapy. John P. Anderson, M.D., Cleveland, Ohio 128

Studies in Thyroid Heart Disease. The Value of Ergotamine in Hyperthyroidism and Its Effect on the Electrocardiogram. Morris W. Lev, M.D., and Walter W. Hamburger, M.D., Chicago, Ill. 134

Society Transactions

American Heart Association, Eighth Annual Meeting, New Orleans, La., May 10, 1932 141

14

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The American Heart Journal

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Symposium on the Thyroid Heart

The papers which follow constitute the program of the meeting of the American Heart Association held in New Orleans on May 12, 1932.

THE MECHANISM OF ADJUSTMENT OF THE CIRCULATION IN HYPERTHYROIDISM (THYROTOXICOSIS)*

WALLACE M. YATER, M.D.
WASHINGTON, D. C.

CERTAIN facts have been learned about the circulation in hyperthyroidism, from both clinical and laboratory investigations, which allow one to speculate intelligently upon the probable mechanism of adjustment of the circulation in that condition. These facts will be briefly given.

Cardiac overactivity is one of the outstanding evidences of hyperthyroidism. It is indicated by both subjective and objective symptoms. The latter are mainly tachycardia, loud heart sounds, enlargement of the area of cardiac dullness and increased pulse pressure.

That there is an increase in the minute-volume output of the heart and a greater velocity of blood flow through the lungs and the tissues has been amply demonstrated both in patients and in animals by competent workers[2, 3, 4, 7, 9, 14, 16, 20, 21, 22, 25] using different experimental methods. The general conclusion has been that there is a fairly close correlation between the oxygen consumption (basal metabolic rate) and the output of the heart in hyperthyroidism. Several workers have noted that the minute-volume output of the heart, however, increased relatively more than the oxygen consumption, so that the oxygen needs of the tissues are supplied without diminishing the oxygen tension of the mixed venous blood. Plummer and Boothby[22] showed that for a given amount of work by patients with hyperthyroidism there is a disproportionate rise in the metabolic rate which requires a similar disproportionate rise in ventilation and in blood-flow. In dogs fed thyroid substance Blalock and Harrison[2] found that the cardiac output increased as the oxygen consumption increased, but that the rate of increase in cardiac output was at first less than that of the oxygen consumption, although later

*From the Georgetown University School of Medicine.

the output increased rapidly and showed a greater relative elevation than the metabolic rate. These facts all indicate that while the demands of the tissues for more oxygen are met by a greater blood flow, the adjustment is not as accurate as it is in the corresponding physiological state, muscular exercise.

The increase in the pulse pressure in hyperthyroidism is a constant phenomenon.[10, 12, 28] It is effected by a moderate increase in the systolic pressure without much alteration of the diastolic pressure. A relationship between the pulse pressure and the basal metabolic rate has been noted,[3, 6, 29] the pulse pressure being greater the higher the basal metabolic rate. The increased pulse pressure, the visible throbbing of the vessels generally, and the frequently observed capillary pulsation are all indicative of general vascular relaxation, which is a necessary concomitant of increased blood flow.

There is an actual increase in the circulating blood volume in hyperthyroidism, as shown by Wislicki[30] and by Chang.[5] This increase may be as great as 30 per cent, and involves the plasma and cellular elements proportionally. It may be due to contraction of the spleen, as in exercise, but there are probably also other factors.

Since tachycardia is such an outstanding and constant feature of hyperthyroidism, it has received considerable attention. It is present even during sleep, and the basal pulse rate when computed with the pulse pressure has been found to give a fairly accurate indication of the degree of elevation of the basal metabolic rate.[3, 13, 19, 24, 26] The cause of the tachycardia has until recently been thought to be a stimulation of the sympathetic nerves, an increased production of adrenalin or a toxic influence on the myocardium. Several groups of investigators have independently proved that these theories are wrong.

J. K. Lewis and McEachern[15] published the results of experiments with rabbits' hearts which showed that the isolated hearts of thyroxinized animals persist beating at an accelerated rate. Priestly, Markowitz and Mann[28] also found that the hearts of thyroxinized rabbits when perfused beat faster than normals.* In an ingenious experiment they demonstrated that the heart of a pup which had been anastomosed to the vessels of the neck of a large dog beat much faster when the large dog was thyroxinized. In a large series of rabbits made acutely hyperthyroid by intravenous injection of thyroxin I[31] found uniformly that the isolated perfused hearts beat much faster for many hours than the hearts of rabbits not thyroxinized. The average rate of the perfused hearts of normal rabbits was 140 per minute and that of the acutely thyroxinized rabbits was 193 per minute, an increase of 38 per cent. The effect of one injection of thyroxin became manifest by the increased heart rate after a latent period of two days and persisted for two weeks.

*The few exceptions were probably due to the fact that the latent period of action of thyroxin had not been recognized.

I noted in these experiments that the hearts of the thyroxinized rabbits were more subject to attacks of arrhythmia and seemed to beat more vigorously than normal. After excision of the sino-auricular node of the perfused hearts of thyroxinized rabbits the heart rate was still greatly increased when compared with controls, and after auriculo-ventricular dissociation was produced by crushing the bundle of His, the ventricles usually continued to beat at an accelerated rate. McIntyre[18] has laboriously completely denervated the hearts of dogs and has found that when the animals were made hyperthyroid the heart beat faster to the same degree as in control dogs. These experiments all showed that thyroxin exerts its effect either upon the muscle fibers or upon the nerve endings in the myocardium. It remained for Cecile Markowitz[17] to show conclusively that thyroxin acts directly upon the muscle fibers. A study was made of the action of thyroxin on tissue cultures of pulsating fragments of heart muscle removed from chick embryos before the appearance of nerve elements in the heart. A progressively greater increase in rate of pulsation occurred, ending in some cases in fibrillation and paralysis.

Some experimental work has been done to compare the survival period of isolated perfused hearts of thyroxinized rabbits with that of hearts of non-thyroxinized rabbits. I studied in this way the hearts of both acutely thyroxinized rabbits and of rabbits kept hyperthyroid for a long period of time. These hearts continued to beat as long as, and possibly better on the average than normal hearts.

With these facts before us we may speculate upon the mechanism by which the circulatory adjustments in hyperthyroidism are made. In order to arrive at a satisfactory conception of this problem it is necessary to review the adjustment of the circulation in the most nearly corresponding physiological state. This state is muscular exercise, since the patient with hyperthyroidism has a circulation rate at rest which is the same as that of an individual undertaking moderate physical exertion.

Bainbridge[1] has written a classical treatise on the physiology of muscular exercise, and this, together with the monograph of Wiggers[28] on the pressure pulses in the cardiovascular system, comprises the main source of information for the following brief account of the circulatory adjustments in exercise.

The oxygen needs of the body per minute during exercise are increased in proportion to the amount of external work performed. This correlation is accomplished by a carefully regulated series of adjustments. In the first place an increase in pulmonary ventilation, which determines largely the oxygen supply of the body, is brought about by a rise in the hydrogen ion concentration of the blood and a greater sensitiveness of the respiratory center; the latter is probably due to the effect upon this center of impulses from the higher centers of the brain flowing out concomitantly with the passage of impulses from the cerebral cortex to

the skeletal muscles. A more rapid circulation rate closely correlated with the degree of increase in pulmonary ventilation is necessary in order that the needs of the tissues for more oxygen may be met. The law of the heart (Starling) states that the ventricles can eject all of the blood which enters them in diastole, and that they do so with the greatest force possible at the time. In exercise more blood is returned to the heart than during rest because of the mechanical squeezing of blood out of the capillaries of the voluntary muscles by the increased activity of the muscles, and also because of the accelerated and augmented respiratory movements, particularly of the diaphragm. In response to a greater venous inflow the heart can increase its output per minute either by a larger output per beat or by acceleration of the pulse rate. The influence of the latter upon the output of the heart per minute is determined by the rate at which the heart fills during diastole. If the venous inflow is adequate, i. e., if it is so rapid that the heart fills almost completely early in diastole, acceleration of the pulse only slightly diminishes the output per beat but greatly increases its output per minute. Thick-walled, well nourished ventricles (such as in athletes) increase their output more by a greater volume per beat than by acceleration of rate. The initial acceleration of the pulse rate at or just before the beginning of exercise is due to the passage of impulses from the higher centers to the vagus center whereby its tone is lessened and to the accelerator nerves whereby their tone is increased. The persistent acceleration of the pulse throughout the period of exercise depends, partly on a continuance of the outflow of impulses from the cerebral cortex to the vagus and accelerator centers, partly on the influence upon the vagus center of the rise in temperature of the body, and partly on the greater diastolic distension of the auricles which reflexly lessens the tone of the vagus center (Bainbridge's reflex). The effectiveness of the larger output in increasing the blood supply to the active muscles, the heart and the brain during exercise is greatly enhanced by constriction of the splanchnic vessels and by dilatation of the vessels of the muscles and heart. The former is brought about primarily and chiefly by the outflow of impulses from the higher centers to the vasomotor center; the latter by the reduction of tone of the arterioles and capillaries directly by the action of acid and other metabolites in the muscles and possibly by the effect of an addition of small amounts of adrenalin to the circulation. The rise of arterial pressure is the resultant of (1) the increased output of the heart, (2) the constriction of the splanchnic vessels, and (3) the dilatation of the vessels in the muscles and skin.

Hyperthyroidism differs from muscular exercise in two main features: (1) the absence of the outflow of impulses from the cerebral cortex to the muscles and the medullary centers, and (2) the absence of increased activity of the muscles, which is perhaps the most important factor in the return of blood to the heart. While an increase in rate and ampli-

tude of respiration is not a prominent feature in hyperthyroidism, it exists, as was first shown by Hofbauer,[11] and is probably due to the effect of an increase in hydrogen ion concentration of the blood upon the respiratory center. To a certain extent this increased respiratory activity aids in the return of blood to the heart. The increased metabolism of the tissues undoubtedly accounts mainly for the general vascular relaxation in the same way as in exercise, and this relaxation is of importance in the acceleration of the return of blood to the heart. The increase in blood volume augments the effect of vascular relaxation and allows the filling of the heart to be adequate in spite of the larger size of the stream-bed.

The main differences between exercise and hyperthyroidism are concerned, therefore, with the mechanism of increase in the cardiac output and of the acceleration of the pulse rate. It would appear from the experimental work reported that the two factors largely responsible for this increase in the minute-volume output of the heart in hyperthyroidism are the acceleration of the pulse rate and the increased vigor of the heart beat. The former has been shown adequately to be due entirely to the effect of an excessive amount of thyroxin in the heart muscle itself and not to the causes of acceleration of the pulse rate which exist in exercise. The increased vigor of beat is indicated by the loudness of the heart sounds, the increased systolic blood pressure in spite of general vascular relaxation and the apparent exaggeration of force of the beat in perfused hearts. A study of the cardiac dynamics of hyperthyroid hearts of animals would be of great value in accurately establishing this point. It is probable that the hyperthyroid heart more completely empties itself early in systole and fills rapidly early in diastole, so that the tachycardia is itself responsible for a great increase in the minute-volume output of the heart. Since the acceleration of the heart rate and the increased vigor of heartbeat are due entirely to the effect of thyroxin upon the heart muscle, it is, therefore, entirely a coincidence that there exists in hyperthyroidism an increased blood flow and velocity of the circulation. Were it not for this fact patients with hyperthyroidism would soon suffer from relative tissue anoxemia and the metabolic rate be decreased. This fact also accounts for the inexact correlation of the rate of oxygen consumption and the increased blood flow.

The ample oxygen supply of the heart itself and the reduction of resistance to blood flow through the tissues probably explain why congestive heart failure is so infrequent until the later decades of life in spite of the increase in amount of work done by the heart. The lack of any great degree of hypertrophy of the heart in hyperthyroidism is probably due to the fact that the peripheral stream-bed is wide open, so that the increased effort of the heart is expended largely upon the increased frequency of the pulse rate and not in overcoming mechanical obstruction to the flow of blood.

Investigators in the field of hyperthyroidism have uniformly passed over the increased rate of circulation by stating that it is due to the greater demands of the tissues for oxygen. To quote a few, Du Bois[8] stated that "Part of the increase in pulse rate is also due directly to the increased metabolism which necessitates a greater blood flow;" Willius and Boothby[28] said that "In view of the constant elevation in the basal metabolic rate in exophthalmic goiter and in adenomatous goiter with hyperthyroidism, it is obvious that there must be an increase in the rate of circulation to meet the increased demand of the tissues for the transportation of electrolites;" and Blumgart, Gargill and Gilligan[3] asserted that "The increased velocity of blood flow in thyrotoxicosis probably occurs to meet the demands of the elevated metabolic rate and not as a result of a toxic effect on the heart." Now it may safely be stated that it is only because of the effect of an excessive amount of thyroxin in the myocardium itself that these "demands" are met.

SUMMARY AND CONCLUSIONS

The facts known regarding the alterations of the circulation in hyperthyroidism have been stated. From these it appears that the increase in the rate of the circulation is a fortuitous rather than a physiological adjustment. It is due mainly to the increase of thyroxin in the myocardium which causes the heart to beat more rapidly and more vigorously. Associated with this are a general vascular relaxation brought about by the local action of metabolites on the arterioles and capillaries, and an increase in the circulating blood volume, due mainly perhaps to contraction of the spleen. There is probably also an increase in rate and depth of respiration, the result of the effect of an increased hydrogen ion concentration on the respiratory center. These factors aid in the more rapid return of blood to the heart.

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(For discussion, see page 143.)

CARDIAC HISTOPATHOLOGY IN THYROID DISEASE. PRELIMINARY REPORT*

CARL V. WELLER, M.D., R. C. WANSTROM, M.D., HAROLD GORDON, M.D., AND JOHN C. BUGHER, M.D.

ANN ARBOR, MICH.

THE cardiac histopathology of thyroid disease has been studied by many observers and very many conflicting reports have been made. Grant[1] found dilated and hypertrophied hearts with little evidence of myocardial degeneration. Many showed a mild myocardial scarring, round-cell infiltration or fatty degeneration, but not sufficient to account for the great disturbance in cardiac function. In some instances there was an acute myocardial necrosis, but this was unusual.

Wilson[2] described the myocardium in eighteen cases of hyperthyroidism as showing swollen fibers with indistinct striations and well marked lipoid changes. Only five patients were under forty years of age. In patients with long-continued pronounced hyperthyroidism, the myocardium shows more advanced fatty changes than are present in the myocardium of individuals of the same age without hyperthyroidism.

In eighteen cases of Basedow's disease and in nine cases of colloid struma with Basedow's disease, Fahr[3] found in the myocardium, fibroblastic proliferation and scars. In cases of colloid struma with cardiac disturbances he described small round cell infiltrations between the muscle fibers and around the small vessels. He regarded these changes as true inflammation. Beyond the infiltration was a slight degenerative fatty infiltration. He stressed the differences in intensity of the changes.

Ceelen[4] found sharply localized necroses with areas of fibroblastic reaction in hearts of Basedow's disease.

No proof of Fahr's findings of infiltrations and true myocarditis could be found by Baust.[5] He recognized only a slight increase in lymphocytes and fibroblasts, but no degenerative changes with fibrosis and scars.

Kerr and Rusk,[6] in a case of hyperthyroidism, described in the myocardium occasional moderate separation of the fibers by edema. One small focus of fibrosis without any evidence of exudative cells in relation to it was seen. In one section a marked perivascular lymphocytic infiltration was seen. No evidence of focal necrosis of the myocardium was observed.

Loos[7] described hypertrophy and dilatation of the heart with microscopical findings of fatty infiltration and lipofuscin formation, areas of round cell infiltration with necrosis, and scars in the muscle. These changes he believed due to toxin from the thyroid and mentioned the re-

*From the Department of Pathology, University of Michigan.

semblance to the multiple necroses in hearts damaged by carbon monoxide and diphtheria toxin.

Askanazy[8] described brown atrophy, degenerative fatty infiltration and an interstitial myocarditis with Basedow's disease; and in eight cases of Basedow's disease, Matti[9] found six with foci of fatty infiltration and one with destruction of muscle fibers, without inflammatory infiltrations. Pettavel[10] reported constant scattered and diffuse fatty infiltration. Simonds[11] in eight cases found only one with fibrous nodules in the muscle. This case was also excluded because of synechia of the pericardium, indicating a complication. Takane[12] had three cases with inflammatory round cell infiltrates in the heart in association with thyroid disease. Hashimoto[13] examined two hearts from exophthalmic goiter patients and found lymphocytic infiltrations between the muscle fibers or around the blood vessels.

Chesky[14] wrote that, while a few cases dying with hyperthyroidism show small scars, fatty degeneration and interstitial and perivascular round cell infiltration, similar lesions are found as a part of the degenerative changes of age in patients without goiter.

The conclusion of White[15] was that there is no constant cardiovascular lesion in thyrotoxicosis. Enlargement and hypertrophy of the fibers is present in some chronic cases, but it is difficult to exclude factors of hypertension and coronary disease. In a few cases necrosis of the myocardium has been found, but this has not been confirmed as a thyroid effect. The heart weight is generally increased only slightly.

Rautmann[16] found hypertrophy and dilatation but no inflammatory or degenerative changes, even in the most severe Basedow cases. In his very complete work he said that the anatomical changes in Basedow's disease are either an hypertrophy-hyperplasia or atrophy-hypoplasia. The hypertrophy and hyperplasia are chiefly met with in the thyroid, thymus, general lymphoid tissue and in heart muscle. The atrophy and hypoplastic changes occur in the adrenals.

METHOD OF INVESTIGATION

In the series of 4200 autopsies at the University of Michigan, there have been 43 instances of exophthalmic goiter and 90 of adenomatous goiter. This material, after a certain amount of selection, forms the basis for the present study. From these two groups there were deleted all those for which permission for a reasonably complete autopsy was not given and also those cases showing any evidence of syphilis, rheumatic fever, infective endocarditis or severe coronary atherosclerosis, on the basis that myocardial changes are exceedingly common in these diseases. As far as possible, known causes of frequent extensive myocardial changes were thus eliminated. Each individual of this greatly shortened autopsy list was then matched as closely as possible with another of the same age, sex and major cause of death, but without thyroid

disease. Thus a definite control series was established, differing from the first only in the factor of thyroid disease. If any distinctive myocardial lesion appears as the result of thyroid disease, it should be evident from the comparison of the two series. In this manner two groups of cases were set up; one with exophthalmic goiters and the other with adenomatous goiters, upon all of which complete autopsies had been performed.

A review of the gross autopsy findings was followed by a microscopical study of the hearts and thyroids from all cases with reference to specific deviations from the normal. In the gross examination, note was made of the total weight of the heart and the thickness of the ventricles. From each heart, at least four and in some cases eight or ten blocks were examined; these included both ventricles and auricles together with all valvular orifices. Where additional sections were needed, as many as seemed necessary to give a complete microscopic representation were prepared.

In reviewing the heart and thyroid material, no attention was paid to previous diagnoses, many of which were separated by thirty-five years in time. Instead, the entire series was evaluated objectively and with as uniform an application of the various criteria as could be employed.

The microscopic examination involved the tabulation of the following 13 items with the indicated connotations:

1. *Atrophy of Myocardium.*—A positive judgment of atrophy was based upon the finding of muscle fibers smaller in size than is normal for the particular age, with oftentimes increased lipoidal pigment about the nuclei and an apparent or relative increase of stroma cells due to condensation of the connective tissue.

2. *Hypertrophy of Myocardium.*—The presence of enlarged fibers with large and hyperchromatic nuclei was taken as the evidence of hypertrophy.

3. *Hypoplasia of Myocardium.*—Fibers of small size but without increase in pigment and without any attendant increase in stroma were considered hypoplastic rather than atrophic.

4. *Zenker's Necrosis.*—This is the classical intracellular coagulation necrosis denoted by palely staining fibers with loss of nuclear differentiation.

5. *Fragmentation of Fibers.*—This phenomenon, probably in itself entirely post-mortem, may indicate a previous change in physical state of the muscle fibers.

6. *Edema.*—In heart muscle, edema is indicated by the swelling and separation by albuminous fluid of the connective tissue cells and fibers.

7. *Cloudy Swelling.*—A swelling of the fiber associated with slight loss in stainability of the nucleus and cytoplasm, where the section generally does not indicate such change to be post-mortem, has been construed to be cloudy swelling.

8. *Fatty Infiltration.*—This is an excess of adipose tissue beneath the epicardium with interdigitation of the outer muscle fibers and fat cells.

9. *Degenerative Fatty Infiltration.*—Unlike the foregoing, degenerative fatty infiltration is an accumulation of fat in many small vacuoles in the cytoplasm of muscle fibers and is associated with degenerative nuclear changes. This is usually most marked immediately beneath the endocardium.

10. *Sclerosis of Small Coronary Branches.*—Cases with important obliterative changes of the large coronary vessels were eliminated from the series. Examination of the small branches was done to assist in making an etiological judgment concerning any areas of fibrosis.

11. *Fibrosis of Myocardium.*—The amount of connective tissue, location and correlation with active inflammation was observed.

12. *Endocardial Sclerosis.*—The positions of these areas as well as the severity of the process were considered in relation to the existence and position of fibroid areas.

13. *Cellular Infiltrations.*—The extent, together with the severity and character of these, was noted.

EXOPHTHALMIC GOITER

The arithmetical mean of the weights of the hearts of both the exophthalmic goiter series and its controls are given in Table I, together with the calculated probable errors of the means and the average measurements of the ventricles. It is to be noted that while there is a difference of 60 grams in the means of cardiac weights, the variability in both series is so great that a difference of the magnitude found may be expected as an error of random sampling. The same conclusion is reached when the

TABLE I

	EXOPHTHALMIC GOITER SERIES	CONTROL SERIES
Weight of Heart, Mean	393 ± 46 grams	323 ± 75 grams
Left Ventricle, Mean	17.2 ± 2.0 mm.	19.0 ± 2.5 mm.
Right Ventricle, Mean	5.6 ± 1.4 mm.	6.5 ± 1.2 mm.

weight of each control heart is subtracted from its companion and the differences treated statistically, the mean preponderance of the exophthalmic goiter hearts over those of the control series being 47 ± 94 grams, there being several cases in which the weight of the control hearts greatly exceeded the ones with which they were paired.

The results of the microscopic examination are given in Table II where it is at once evident that while there are several pathological features

TABLE II

EXOPHTHALMIC GOITER	GOITER CASES		CONTROLS	
	NUMBER	PER CENT	NUMBER	PER CENT
Total cases used in microscopic examination	35	100	35	100
Atrophy of myocardium	3	8.6	12	34.3
Hypertrophy of myocardium	23	65.7	21	60.0
Hypoplasia of myocardium	21	60.0	7	20.0
Zenker's necrosis	8	22.8	4	11.4
Fragmentation of fibers	5	14.3	7	20.0
Edema	11	31.4	7	20.0
Cloudy swelling	25	71.5	22	62.8
Fatty infiltration	15	42.8	17	48.6
Fatty degenerative infiltration	24	68.6	22	62.8
Sclerosis of small coronary branches	16	45.7	16	45.7
Fibrosis of myocardium	28	80.0	18	51.5
Endocardial sclerosis	31	88.6	18	51.5
Cellular infiltrations	11	31.4	6	17.1

having a high incidence in the exophthalmic goiter series, there are only four items which are at all impressive in comparison with similar findings in the controls. These are: hypoplasia of myocardium, fibrosis of myocardium, endocardial sclerosis and cellular infiltrations. The evidence upon which the conclusion of hypoplasia was based was found only in the right ventricle and, in general, was not a very outstanding feature.

Of the exophthalmic goiter hearts, 80 per cent showed patches of fibrosis which for the most part were associated with endocardial sclerosis and were found chiefly in the left ventricular wall and in the papillary muscles. These changes had no definite vascular associations although frequently they would be adjacent to small vessels. The lesions

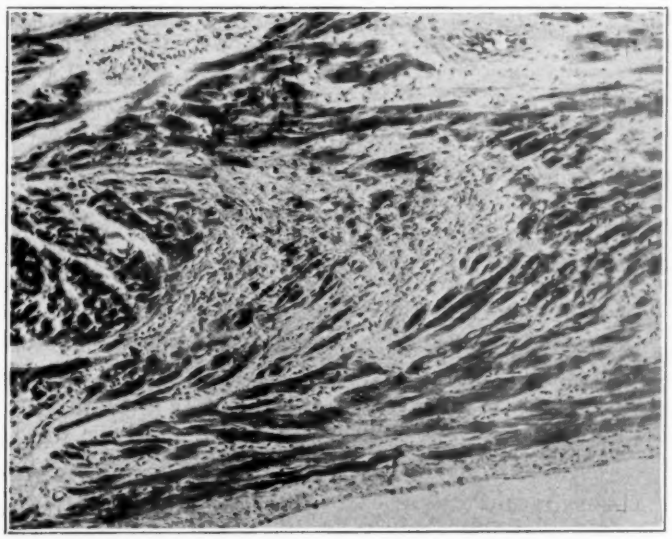

Fig. 1.—A-249-AJ. Active inflammatory focus with fibrosis beneath endocardium. ×95.

were usually small and for the most part had not been seen in the gross examination. In contour, they were irregular, the peripheral strands interdigitating with the surrounding muscle fibers, but very few of them showed any evidence of survival of muscle fibers within the area of fibrosis. Concerning the character of the lesions, no specific features could be determined save that they were not related to vascular obliteration. In view of the preliminary exclusion of such cases from the series, it can be positively stated that these lesions were not due to syphilis, rheumatic fever or coronary disease.

Of the eleven cases of the exophthalmic goiter series showing cellular infiltrations, six showed only subepicardial foci of wandering cells, this being also the localization of infiltrations shown by the six controls. Of the remaining five exophthalmic goiter cases, one showed such an active and unusual myocarditis that it merits more detailed consideration.

This patient, a woman 41 years of age, was admitted to the University Hospital in stupor, and the meager history was obtained from relatives. She had had definite goiter with exophthalmos for ten years with a marked increase of symptoms three weeks before entering the hospital and with vomiting for the last week of that pe-

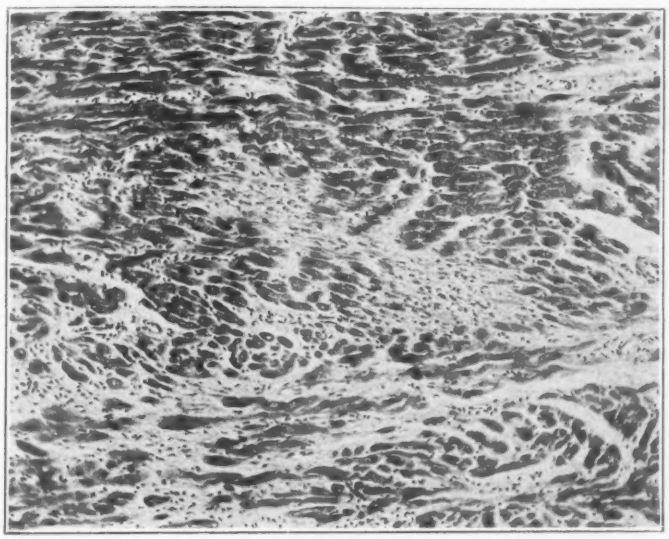

Fig. 2.—A-249-AJ. Small inflammatory focus deep in myocardium. ×95.

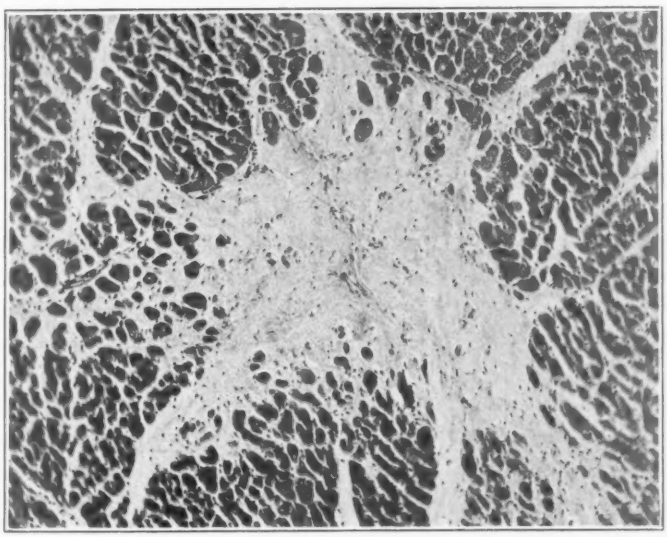

Fig. 3.—A-249-AJ. Healed lesion. Hyaline connective tissue. No active infiltration. ×95.

riod. On examination there was definite cardiac enlargement, a systolic murmur at the apex, a pulse of 110, and a blood pressure of 160/75 mm. Electrocardiogram showed a sinus tachycardia with inverted T-waves in leads I and II. A diagnosis of thyroid crisis was made, intensive lugolization and digitalization were started and

x-ray administered to the thyroid. The condition grew worse and the patient died six days after entering the hospital.

At autopsy the heart was found to weigh 400 grams and measured 11 × 11 × 7.5 cm. The left ventricle was 25 mm. in thickness; the right ventricle measured 11 mm.

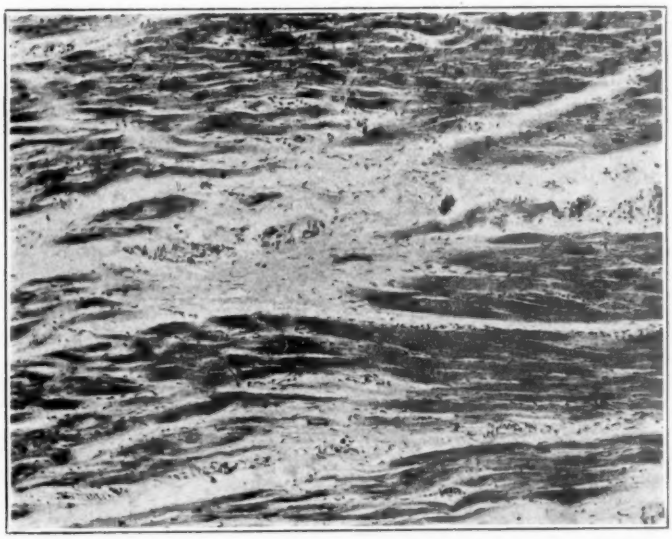

Fig. 4.—A-125-Z. Small area of fibrosis. No active inflammation. ×95.

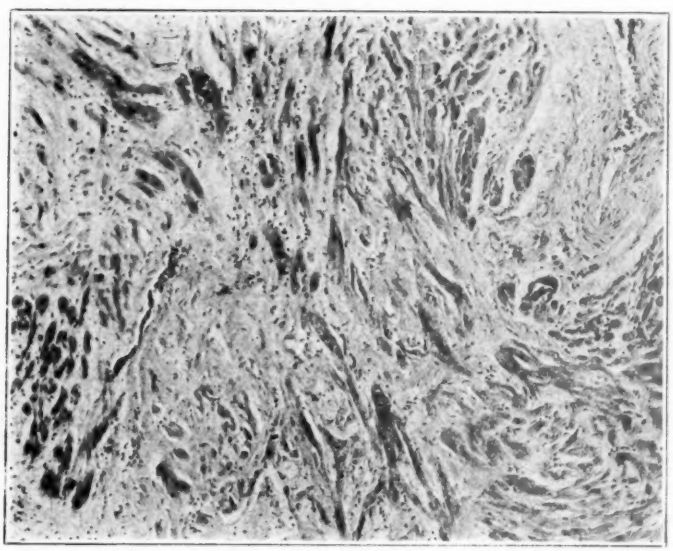

Fig. 5.—A-125-Z. Extensive fibrosis with survival of muscle fibers. ×95.

Both ventricles were dilated. Microscopically, a moderate hypertrophy of the muscle fibers and a moderate atherosclerosis of the larger coronary arteries were found. Most striking, however, were the many focal lesions occurring throughout the myocardium, even that of the auricles. These were strictly nonpurulent and could be

found in all stages from focal necroses of the muscle fibers with lymphocyte and plasma-cell infiltrations to old and somewhat hyaline patches of fibrosis. The lesion was essentially a fibroblastic proliferation in response to focal necrosis rather than a diffuse interstitial fibrosing process. Various stages in the evolution of these fibroid areas are shown in Figs. 1 to 3.

In four other hearts, cellular infiltrations associated with patchy fibrosis were found, but in none of these were early lesions seen and the wandering cells were relatively sparse. In general, the fibroid regions resembled the healed lesions of the case showing active myocarditis and likewise there was no obvious explanation of their presence. Typical fibroses are shown in Figs. 4 to 6.

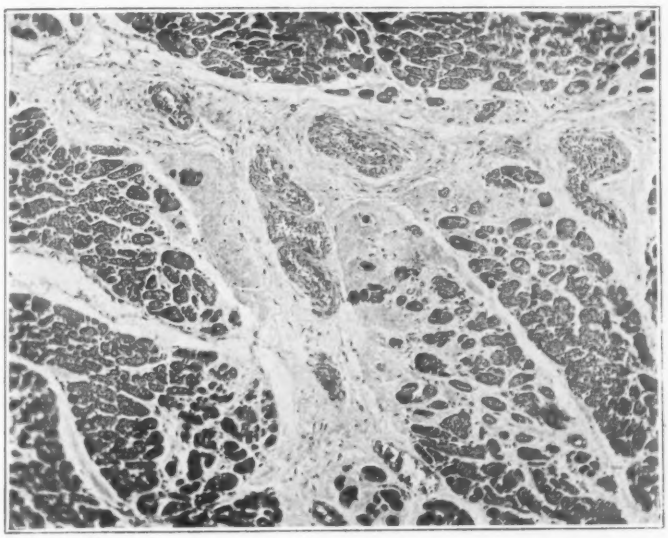

Fig. 6.—A-126-AE. Old perivascular fibrosis extending into myocardium. ×95.

The one case of active myocarditis agrees with those previously described by Fahr, but in this series, unless the numerous fibroses are assumed to be healed focal lesions of that variety, it is not as frequently occurring as Fahr found to be the case in those he studied. It is a reasonable explanation that the numerous fibroid foci are actually the end result of a distinctive myocarditis, but there is no positive proof of this.

With respect to the other pathological changes in the hearts of the exophthalmic goiter series, the incidence of necrobiotic changes such as cloudy swelling and degenerative fatty infiltration is high, but the control series shows correspondingly high values for these items. This is undoubtedly due to the circumstances attending death, and further elucidation of this point is given in Table III where a tabulation of the immediate causes of death shows 21 of the 35 cases to have died of severe infections in which such retrogressive phenomena are the rule.

TABLE III
EXOPHTHALMIC GOITER

19 Males, average age at death	43.6 years
21 Females, average age at death	41.5 years
40 Cases, average age at death	42.5 years
Immediate Causes of Death:	35 cases
Exophthalmic goiter only	2 cases
Cardiac insufficiency	9 cases
Pneumonia	17 cases
Other infections	4 cases
Lymphatic leucemia	1 case
Cerebral hemorrhage	1 case
Asphyxia	1 case
Average duration	3.4 years
Auricular fibrillation	15 cases
Average basal metabolic rate	+48%
Maximum basal metabolic rate	+90%
Minimum basal metabolic rate	+14%

ADENOMATOUS GOITER

After pursuing the same eliminations as in the exophthalmic goiter series, 55 complete autopsies remained showing adenomatous goiters and no evidence of syphilis, rheumatic fever, infective endocarditis or advanced atherosclerosis of the larger coronary arteries. For each of these a control was selected following the same procedure as in the exophthalmic goiter study. The same tabulation of microscopic findings was employed, and the results are given in Table IV. From the data, it appears that no significant difference between the two series existed save in respect to cellular infiltrations. However, in both series, these in-

TABLE IV
ADENOMATOUS GOITER

	GOITER CASES		CONTROLS	
	NUMBER	PER CENT	NUMBER	PER CENT
Total cases used in microscopic examination	55	100	55	100
Atrophy of myocardium	18	33	14	26
Hypertrophy of myocardium	42	76	42	76
Hypoplasia of myocardium	12	22	9	16
Zenker's necrosis	0	0	2	4
Fragmentation of fibers	8	15	8	15
Edema	21	38	16	29
Cloudy swelling	37	67	37	67
Subepicardial fatty infiltration	34	62	42	76
Fatty degenerative infiltration	49	89	50	91
Sclerosis of small coronary branches	22	40	18	33
Fibrosis of myocardium	35	64	40	73
Endocardial sclerosis	39	71	42	76
Cellular infiltrations	17	31	8	15

filtrations were nearly all subepicardial in location; and considering the fact that two-thirds of the adenomatous goiter individuals died of severe infections such as pneumonia and purulent peritonitis, this difference is also probably meaningless. The very high incidence of 89 per cent for degenerative fatty infiltration is in accordance with the reported high figure for that change in this disease, but this is at once discounted by finding it in 91 per cent of the controls.

As far as this evidence goes, we are thus forced to the conclusion that no definitely demonstrable cardiac lesion occurs as the result of adenomatous goiter. All of the changes previously described in such cases can be verified in this series, but when rigidly controlled, it is found that such changes are due to the concomitant conditions of illness rather than to the presence of the thyroid disease.

SUMMARY AND CONCLUSIONS

1. A morphological study of the hearts of 35 patients with exophthalmic goiter showed, with but few exceptions, no gross or microscopical pathological changes not equally represented in a carefully matched control series.

2. The exceptions found were (1) a relatively higher incidence of myocardial fibrosis, endocardial sclerosis, and cellular infiltrations in the series with exophthalmic goiter and (2) one case in the series of 35 which showed an active focal myocarditis for which no etiological factor could be ascertained other than the hyperthyroid state.

3. Twenty-eight, or 80 per cent of the exophthalmic series showed areas of myocardial fibrosis, as compared with 51.5 per cent of the control series. It is impossible to determine to what extent, if any, such areas of fibrosis may be the result of an active myocarditis of the type found in the single case.

4. The hearts of 55 cases of adenomatous (nodular) goiter failed to show any significant difference in the incidence of pathological changes as compared to a matched nongoitrous control series.

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(For discussion, see page 143.)

A STUDY OF THE HEART IN HYPERTHYROIDISM*

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WHILE the opinion commonly held is that the cardiac phenomena in hyperthyroidism are due to a specific toxin produced as a result of the disease and acting specifically on the myocardium, yet those who have had occasion to study the literature dealing with this question will have been impressed with the lack of unanimity, indeed the frank contradictions, which characterize the problem. The concept of structural change as a basis for the cardiac phenomena is in reality founded upon a very small number of reliable clinical reports or experimental protocols. Furthermore, great stress should be laid on the absence of any satisfactory control series of macroscopic and microscopic observations on "presumably" normal hearts in human beings and animals. The literature in question has been carefully studied and reviewed up to the end of 1930 by the present authors in previous papers, to which reference may be had.[1, 2] It may be stated in brief that in the majority of instances, apart from hypertrophy, either no change was found or else the changes did not exceed those which the present authors have shown to occur in a series of "normal" hearts. In a small number of cases, however, there have been described quite extensive diffuse or local lesions in the myocardium, which have been considered specific. This brief review of the literature serves whether it be applied to papers dealing with human autopsy material or to those discussing the results of experimental observations on rabbits, guinea pigs, rats, etc., after being fed or injected with different preparations of the thyroid gland. Papers appearing since 1930 have, with one exception,[3] agreed on the absence of any specific myocardial lesion.

It is pertinent to turn for a moment from human and experimental pathology and to examine the clinical picture of the hyperthyroid patient with cardiac disease. Thus one may ascertain whether there is here anything to lead one to presume a structural change as producing the phenomena. When this is done it is found that far from supporting the hypothesis of a structural change, clinical observations tend definitely to rule it out. Thus many authors testify to the fact that when congestive heart failure appears in hyperthyroidism, there is usually some other organic factor, rheumatic carditis, syphilis, or the like, which tends to lower the cardiac reserve. Again, auricular fibrillation cannot be said to indicate, of necessity, structural alteration, for not only can it be produced with ease (as by asphyxia) in the laboratory without any ac-

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companying structural change, but together with other manifestations of serious cardiac embarrassment, it may, in the absence of co-existing organic heart disease, vanish literally overnight following satisfactory response to therapy.

In order to throw some light upon this problem with its mass of conflicting evidence, recourse has been had to two methods; first, examination of autopsy material together with full clinical records and autopsy protocols, and second, animal experimentation. In both cases what was believed to be an adequate number of control examples was studied. The results of these two investigations will be given separately.

AUTOPSY STUDIES

Twenty-seven autopsy cases were studied. Abstracts were made from clinical histories and autopsy protocols. Wherever possible, the gross autopsy material was examined and further microscopical preparations made for fat stains or routine haematoxylin and eosin stain. In every case sections of the heart and other important organs were available. The heart sections included, at least, part of the left ventricle, the mitral valve, and the left auricular wall. Positive findings in all other organs were recorded.

One hundred and fifty controls were studied; twenty-five for each of the six decades over which the cases of hyperthyroidism were scattered. These one hundred and fifty cases were chosen consecutively from the autopsy records, omitting cases of goiter, syphilis, profound anemia, septicemia, and local disease in and around the heart. Those cases in which coronary sclerosis was mentioned in the protocols were also discarded. Microscopical sections from the myocardium were examined in each instance.

The twenty-seven cases could be divided into three groups, according to the degree of alteration observed in the hearts. In none of the three groups was there any significant increase in the brown atrophy (lipochrome) granules. In the first group were fourteen cases in which the changes found were present also in normal hearts from the same age groups.

In the second group eight cases appeared, showing moderate changes such as intermuscular scarring or increased perivascular fibrosis, slight cell infiltration, and alterations in staining reaction or contour of muscle-fibers. Changes similar in kind, if not in degree and frequency, were found in normal hearts of the same age periods, which hearts had given no evidence of disturbed function during life. Because of their non-specific character and their occurrence in numerous control cases, it seems impossible to ascribe to these lesions the cardiac phenomena observed clinically. In both hyperthyroid and control cases all changes except the cell infiltration were more common in the later decades of life. It is conceivable that they may be accentuated as a result of prolonged

overwork in the presence of the profound metabolic changes demonstrable in the tissues of the hyperthyroid patient.

Finally, five cases fell into the third group. These exhibited profound changes, consisting of areas of muscle-fiber destruction with replacement by connective tissue, infiltration by lymphocytes and monocytes with occasional polymorphonuclear leucocytes. Old intermuscular and perivascular scars were sometimes seen. Of these five, three had co-existing organic heart disease, two rheumatic fever and one syphilitic aortitis, which might be held responsible for the lesions. In the other two there was nothing to account for the changes. One of them showed extreme diffuse change with destruction of muscle-fibers and mononuclear cell infiltration.

Out of the twenty-seven cases, definite hypertrophy occurred in sixteen. Dilatation was a frequent finding and might well explain the enlargement encountered clinically.

No satisfactory relation could be found between the clinical symptoms and the structural changes in the heart. Thus, of seven patients dying with congestive failure, two showed marked changes, two moderate changes, and three were normal. In both of those in which marked changes were present there was co-existent organic heart disease. Again, of the six patients with co-existing heart disease, five died with congestive heart failure and in only two cases was congestive failure present without organic cardiac disease. The duration of the hyperthyroidism bore no relation to the structural changes found in the microscopical preparations.

EXPERIMENTAL STUDIES

In the experimental work both rabbits and guinea pigs were used. Injections of thyroxin (Roche) were given intramuscularly on alternate days. Guinea pigs received doses of 0.1 to 0.17 mg. over 4 to 83 days; rabbits received doses of from 0.1 to 0.35 mg. over 2 to 13 days. The weight, temperature, and heart rate were recorded every day and the degree of hyperthyroidism judged by loss of weight, increase in cardiac and respiratory rate, diarrhea, apprehensiveness, and muscular weakness. Evidences of hyperthyroidism appeared usually thirty-six to forty-eight hours after the first injection and progressed with succeeding doses. Of the animals that died, only those so recently dead as still to be warm were included in the series. The majority were killed. Tissues were fixed in Zenker-formol or formalin. In every case both auricles and ventricles were examined and in most cases preparations were made from adrenals and lungs. In the case of both guinea pigs and rabbits, a series of normal hearts was examined in order to ascertain the variety and degree of changes present in the normal animal.

Seventeen injected guinea pigs were examined together with twenty controls. Of the seventeen experimental animals, nine were free from

apparent terminal infection and of these eight showed no lesions, while one, which singularly enough had given the least evidence of hyperthyroidism, showed a small area of dead muscle-fibers with lymphocytic infiltration. There was no other demonstrable change. It may be that this animal had an unrecognized area of lung infection similar to those found in the other eight animals in which almost identical cardiac lesions were found. These eight animals showed a spontaneous pneumonia due apparently to *Pasteurella bronchisepticus*. Moreover, all showed definite myocardial damage with masses of necrotic pink-staining muscle surrounded by monocytes and pseudo-eosinophils. In later stages this lesion was represented by areas of vacuolated and shrunken fibers with collapsed stroma, lymphocytes, and fibroblasts. Other lesions included an overwhelming proliferation of sarcolemma cells around degenerated muscle-fibers; also an extreme vacuolation of the muscle-fibers so that these appeared to be "blown out." One can only believe from these results that the hyperthyroidism *per se* produces at most very slight lesions, though it may have an adjuvant action, preparing the myocardium for the attack of any terminal infection or toxemia.

Forty-four injected rabbits were examined together with forty-three controls. The lesions found in 13.7 per cent of the controls (i. e., normal rabbits from stock) were surprising in degree and kind. The lesions in the experimental animals differed only in quantity and that slightly from those found in the control series. Here again one is forced to conclude that thyroxine, though given in amounts sufficient to render the animals markedly hyperthyroid, produces at most only insignificant morphological changes in the myocardium.

DISCUSSION

Both the autopsy and the experimental material therefore point to the fact that hyperthyroidism by itself produces no specific lesions in the myocardium. It is conceivable that damage produced on the one hand by physiological wear and tear and on the other by any associated infection or other disease tends to be more accentuated in the individual with hyperthyroidism than in the normal one. Whether such cases as those described by Fahr,[4] Goodpasture,[5] and Lewis,[3] and occurring twice in the present series, in which profound damage is present without any co-existing complicating disease—whether such represent the results of a toxin derived from the thyroid gland and circulating in the blood, it is difficult to be certain. But the evidence at present points against the occurence of a specific causal toxin producing specific myocardial lesions.

It is felt that in the past too much emphasis has been laid upon the morphological changes in the myocardium with consequent neglect of important alterations in the metabolism and function of the muscle-fibers. In this connection attention may be drawn to the recent work

on the glycogen content of voluntary and cardiac muscle in hyperthyroidism.[6, 7] It has been shown that in the experimentally produced disease no glycogen can be found microscopically or by analysis in the myocardium. As a result of this, rigor mortis sets in immediately, a fact which the present authors can abundantly confirm from their experimental experience. It is well-known that the withdrawal of glycogen from cells normally well supplied with it renders them more liable to injury, injury to which they react by diminished function and actual structural change and death. This problem has been well examined in the case of the liver and one may well believe that similar reasoning can be applied to the myocardium. It seems more than probable that a close examination of this and other physiological problems will bring one nearer to the understanding of the cardiac abnormalities in hyperthyroidism.

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THE HEART RATE DURING SLEEP IN GRAVES' DISEASE AND IN NEUROGENIC SINUS TACHYCARDIA*

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A PERSISTENTLY rapid heart rate is one of the most characteristic features of Graves' Disease. It is caused chiefly by one or all of the following factors: The increased consumption of oxygen by the tissues which necessitates an increased minute-volume flow of blood to which the acceleration of heart rate contributes; the action of the altered thyroid secretion on the heart itself[1]; the action of the altered thyroid secretion on the sympathetic nervous system leading to a neurogenic tachycardia superimposed on the basic acceleration determined by the first two factors.

The presence of an unexplained sinus tachycardia properly suggests the existence of Graves' Disease; yet in many instances such a rapid heart rate is due solely to neurogenic or psychogenic factors. Neurogenic sinus tachycardia is caused only by a disturbance of the nervous regulation of the heart, which interferes with the usual well regulated reflex adaptation of cardiac function to the needs of the body.

The determination of the basal metabolism is useful in distinguishing these two types of tachycardia, for only the thyrogenic tachycardia is associated with an elevated basal metabolism. Although there is a close parallelism between the basal pulse rate and metabolism in successive observations on the same individual,[2] the relationship between the pulse rate and metabolism of different individuals is not so marked. The pulse rate cannot be taken as an absolute index of the activity of a given case of Graves' Disease, although an extreme degree of tachycardia suggests a greatly increased metabolism.[3] A marked discrepancy, particularly the association of a slow pulse with a high basal metabolic rate challenges the accuracy of the basal metabolism estimation. A heart rate that is unduly rapid as compared to the basal metabolism is usually determined by reflex acceleration.

Another method of differentiating neurogenic from thyrogenic tachycardia is by the determination of the minimum heart rate during sleep.[4] I have shown elsewhere[5] that the minimum heart rate during sleep is the best measure of the intrinsic chronotropism of the heart. The average minimum heart rate during sleep of normal males is 53, of females 58 a minute. In patients with Graves' Disease the high metabolism and the direct action of the thyroid secretion on the heart muscle persist during the full twenty-four hours. Reflex excitation by way of the

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Read by Title.

unstable sympathetic nervous system diminishes greatly during sleep, so that with the abatement of these neurogenic overtones there will be a slight reduction in heart rate during sleep. The residual tachycardia is a rough measure of the degree of thyroid intoxication. A pure neurogenic tachycardia, on the other hand, almost disappears during sleep so that the figures approach those of normal individuals.

In this paper are presented studies of waking and sleeping heart rates recorded continuously with the cardiotachometer[6] of nine patients with Graves' Disease and ten with neurogenic sinus tachycardia. Observations were begun in the late afternoon and were continued through the night until the next morning. In a few cases the heart rate was recorded continuously for twenty-four hours. In Table I are recorded the minimum sleeping, and the basal heart rates, as well as the usual range of rate while awake.

TABLE I
HEART RATES

	CASE	MINIMUM SLEEPING	BASAL	USUAL RANGE WAKING	BASAL METABOLISM
Females:	A9	77	84	100	+28
Graves' Disease	A16	78	82	100 to 110	+23
	A4	79	86	90 to 100	+20
	A8	88	91	90 to 100	+33
	A17	98	106	110 to 120	+58
	A3	114	127	120 to 140	+77
	Av.	*89*	*96*		
Neurogenic	D2	64	112	100 to 130	
Tachycardia	D4	73	82	90 to 100	−2
	D5	53	73	90 to 100	
	D6	71	75	80 to 95	
	D7	64	70	85 to 100	
	D8	78	86	100 to 110	
	D10	59	73	90 to 100	
	Av.	*66*	*81*		
52 Normal cases	*Av.*	*58*	*70*		
Males:	A6	81	88	100 to 120	+36
Graves' Disease	A12	91	108	110 to 120	+55
	A13	95	105	110 to 120	+57
	Av.	*89*	*100*		
Neurogenic	D1	72	77	86 to 110	+13
Tachycardia	D3	62	68	80 to 110	
	D9	52	67	80 to 110	
	Av.	*62*	*71*		
51 Normal cases	*Av.*	*53*	*61*		

The patients with Graves' Disease have high minimum sleeping heart rates, over 30 beats a minute higher than those of normals. The minimum sleeping heart rate in general parallels the basal metabolic rate. The differences between the basal heart rate, and the minimum sleeping rate are rather small, demonstrating the slight reduction in rate during sleep. Although the range of heart rate of patients with neurogenic tachycardia during waking hours often approximates that of patients with Graves' Disease, during sleep the rate reaches minimum levels that approach those of normals. In this they differ sharply from the patients

with Graves' Disease. The table also shows that the minimum heart rate during sleep is a better guide than the basal heart rate in determining the significance of a given tachycardia. This is particularly well brought out in Case D2 in which the basal rate is 112 but the minimum sleeping rate is 64.

In these patients it is often difficult to obtain relaxation sufficient to permit accurate estimation of the basal metabolism and the basal heart rate. It is well known that basal metabolism estimations, unless performed with the greatest care, are apt to be too high. In such cases the determination of the minimum heart rate during sleep serves as an excellent check on the accuracy of the basal metabolism test. At times this record is obtained with difficulty, for patients with Graves' Disease often have a very light and restless sleep.

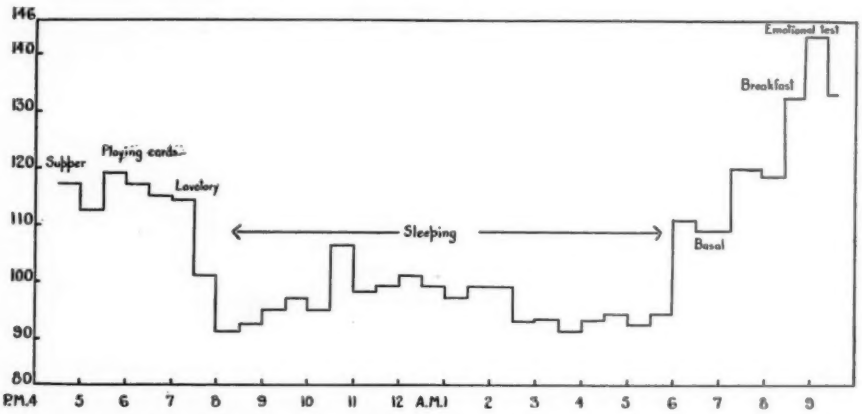

Fig. 1.—Seventeen hour record of heart rate of a man with Graves' disease. Basal metabolism + 55 per cent.

Fig. 1 represents a 17-hour record of the heart rate of a man with Graves' Disease. He had had mild symptoms for a number of years, which had become greatly aggravated during the preceding three months. His basal metabolic rate eleven days before the study of his heart rate was plus 55 per cent. The heart rate during sleep dropped to a minimum of 91, which is almost 40 beats higher than the average for normal individuals. Yet this minimum is low compared to his heart rate while he was awake, and in particular to his basal heart rate. It suggests that he was not fully relaxed at the time the basal heart rate and basal metabolism were measured.

Fig. 2 is the curve of heart rate of a negro woman with Graves' Disease, before and after operation. She, too, presented the classical symptoms of Graves' Disease. Her basal metabolism at the time of the first study was plus 28 per cent. Her heart rate, as observed at her visits to the clinic, ranged from 110 to 130. During the period of observation with the cardiotachometer the rate was lower and reached

a minimum of 77 during sleep, which, however, was 20 beats higher than the average minimum sleeping rate of normal women. Three and one-half months later, which was two months after subtotal thyroidectomy, the pulse was still rather labile but reached a minimum of 65 during sleep.

Fig. 3 represents the heart rate of a woman aged 49 who during a period of observation of over a year at the dispensary had always exhibited heart rates ranging from 112 to 150. She had no signs of

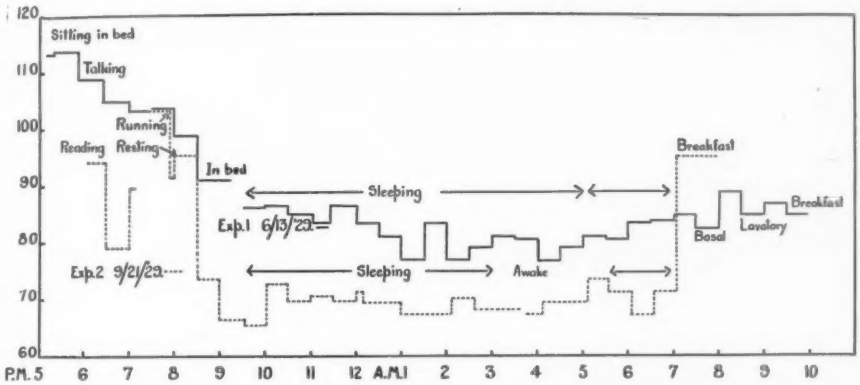

Fig. 2.—Curve of heart rate of a woman with Graves' disease. Solid line, basal metabolism + 28 per cent. Dotted line, two months after subtotal thyroidectomy.

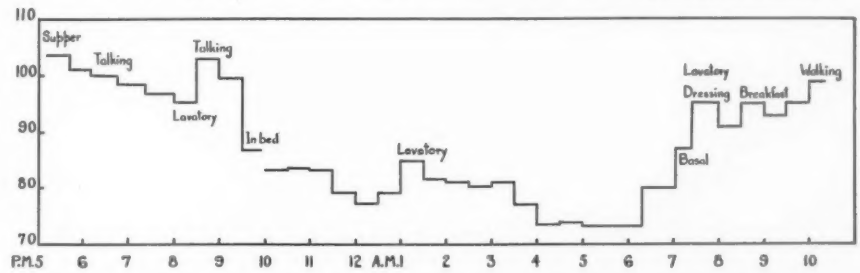

Fig. 3.—Seventeen hour record of heart rate of a woman with neurogenic sinus tachycardia.

Graves' Disease but had a mild systolic hypertension of about 160/80 with slight left ventricular enlargement, and a basal metabolism of minus 2 per cent. During her period of observation with the cardiotachometer, when she was more relaxed and not so conscious that she was being observed, the heart rate did not reach the high figures that had been noted during her visits to the dispensary. It ranged round 100. During sleep it dropped to a minimum of 73. This case also illustrates the fact that in patients with neurogenic sinus tachycardia the heart rate during sleep does not descend to quite as low a level as in normal individuals. This point deserves further study, for it may offer a clue to the better understanding of the mechanism of this disorder.

SUMMARY

The heart rates of patients with Graves' Disease and with neurogenic sinus tachycardia have been studied with the cardiotachometer. In Graves' Disease there is little reduction in heart rate during sleep, and the minimum sleeping rate is on the average over 30 beats higher than that of normal individuals. In neurogenic sinus tachycardia the heart rate shows a marked reduction during sleep, but does not quite attain the low level observed in normal individuals. The measurement of the heart rate during sleep is of diagnostic value in distinguishing thyrogenic from neurogenic tachycardias, and also serves as a rough check on the reliability of the basal metabolism determination.

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THE SIGNS AND SYMPTOMS OF HEART CHANGES IN TOXIC GOITER*

A Clinical Study of 148 Cases

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THIS is a study of 117 cases of toxic goiter† which were observed in the Colorado General Hospital between February 24, 1925, and April 1, 1932, and of 31 cases seen in private practice in the same district and in practically the same period, a total of 148 cases reveiwed from the standpoint of signs and symptoms of heart involvement in toxic goiter. The Colorado General Hospital material was selected because it represents the combined records of the medical and surgical services of this institution and the work of eight attending physicians and surgeons with their staff officers. It thus represents a cross section of the observations of the average teaching hospital in this country, with due allowance for the fact that Colorado is not in a goiter area and that all of these patients lived at an average elevation of at least one mile above sea level.

In the tables relating to symptoms and signs other than pulse and blood pressure findings, and in their discussion, there has been no attempt to classify into types of goiter as exophthalmic and toxic adenoma, the presence of excessive or abnormal thyroid secretion being considered sufficient for inclusion in our series; where such a differentiation was made the biopsy diagnosis was accepted in all cases operated upon.

Sex.—There were 32 males and 116 females.

Table I

Age Distribution of Cases Showing Excessive or Abnormal Thyroid Secretion

	up to 20	20-30	30-40	40-50	50-60	60-70	total
Age when first seen	7	29	35	43	24	10	148
Exoph. goiter Age when first seen	6	21	25	18	9	2	81
Toxic adenoma Age when first seen	1	6	6	21	13	7	54
Mixed group Age when first seen		2	4	4	2	1	13
Signs of heart disease	5	20	18	37	19	7	106
Symptoms of heart disease	7	23	26	37	20	5	118
Large heart	1	8	7	11	14	3	44

*From the University of Colorado School of Medicine and Hospitals.
†Where the term toxic goiter appears in this paper, it refers to exophthalmic goiter or toxic adenoma of the thyroid, no attempt being made to differentiate the two types.

Age.—The average age of the males was forty-two years; the oldest was seventy and the youngest twenty-three. The average age of the females was thirty-nine years, the oldest being sixty-five and the youngest sixteen.

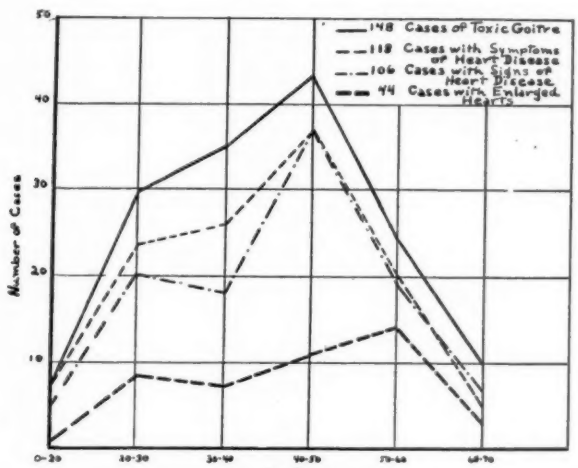

Figure I.

Age-Frequency Curves of Signs and Symptoms of Heart Disease

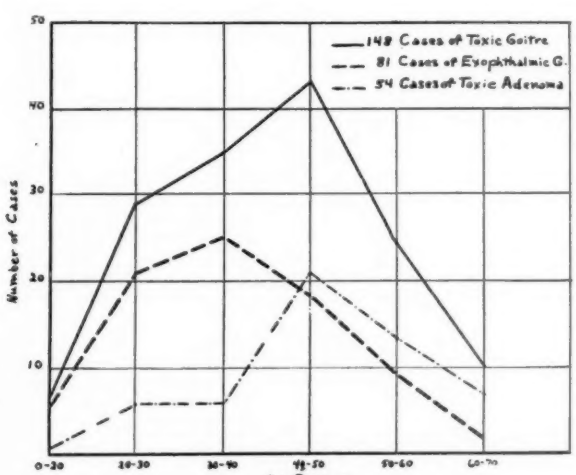

Figure II

Thyrotoxic Symptoms.—The symptoms complained of, which could reasonably be ascribed to the dysfunction of the thyroid gland, quite aside from any resultant or co-existent heart disturbance, were as follows: nervousness, weakness, loss of weight, loss of strength, easy fatigue, tremor, sweating, flushing and sensations of warmth, increased

appetite, gastro-intestinal symptoms, eye symptoms, hyperpyrexia, emotional instability, insomnia and related manifestations of nervous irritability, swelling of the gland or neck, and such pressure manifestations as dysphagia, choking, cough, etc.

Symptoms of Heart Involvement in 148 Toxic Goiter Cases.—Dyspnea on exertion was the most frequently noted symptom, being present in 83 cases, or 56 per cent. Orthopnea was noted in 9 cases, or 6 per cent. Palpitation ranked next in importance, being present in 78 cases, or 53 per cent. Forty-seven cases (32 per cent) complained of tachycardia in addition to some other symptom usually accepted as indicative of heart disease. Next in order appeared swelling of the feet or ankles (37, 25 per cent), precordial or substernal pain (18, 12 per cent), heart consciousness (4, 3 per cent), dizziness (11, 7 per cent), and cardiac irregularity (5, 3 per cent).

In this series of 148 cases of thyrotoxic disease it was found that symptoms of heart disease appeared in 118 cases (approximately 80 per cent) in the following order of frequency:

TABLE II

HEART SYMPTOMS IN 148 CASES OF TOXIC GOITER
PERCENTAGE TABLE

Dyspnea or shortness of breath was complained of in	83 cases,	56%
of which orthopnea was noted in	9	6%
Palpitation	78	53%
Tachycardia	47	32%
Swelling of ankles	37	25%
Precordial or substernal pain	18	12%
Dizziness	11	7%
Irregularity of heart	5	3%
Heart consciousness	4	3%

Signs.—Tachycardia was found on examination more than twice as frequently as complained of, being present in 107, or 72 per cent. This can hardly be accepted as a sign of heart involvement in toxic goiter, but merely as a measure of the physiological response to increased demands. The pulse was normal (70-90) in 23, 16 per cent, and slow (below 70) in one case.

The heart was noted as enlarged (indicated by the position of the apex beat, the percussion borders, x-ray, or any combination of these three methods) in 44, or 30 per cent; the average age of this group was 41.18 years. In 29 cases heart films were taken. In Table I and Fig. I it is seen that heart enlargement was noted chiefly in the fifth to sixth decades, although the peak of age incidence for the total series fell in the fourth and fifth decades (see Fig. I).

A systolic murmur at the apex was noted in 59 cases (40 per cent); in Table III we present the available data as to transmission.

The systolic blood pressure was 160 mm. or above in 29 cases and the diastolic was 90 or above in 33 cases. The age periods in which these occurred is shown in Fig. IV.

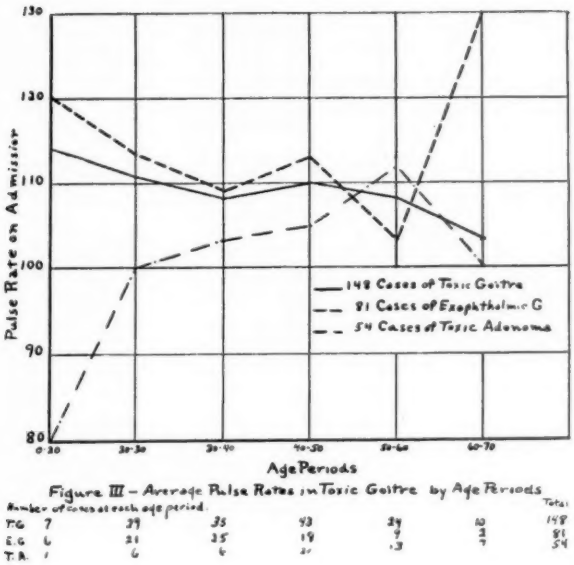

Figure III – Average Pulse Rates in Toxic Goitre by Age Periods

Number of cases at each age period.							Total
T.G.	7	29	35	43	24	10	148
E.G.	6	21	25	19	7	3	81
T.A.	1	6	6	21	13	7	54

Table III

Heart Signs in 148 Cases of Toxic Goiter
Percentage Table

Normal heart, no signs other than tachycardia,	in 34	cases,	23%
Normal pulse, 70-90,	23		16%
Tachycardia, above 90,	107		72%
Heart enlarged	44		30%
Blood pressure, systolic 160 or above,	29		20%
diastolic 90 or above,	33		22%
Systolic murmur at apex or pulmonary area,	59		40%
Systolic murmur at apex or pulmonary area, transmitted,	24		16%
Systolic murmur at apex or pulmonary area, not transmitted	9		6%
Systolic murmur at apex or pulmonary area, no note as to transmission,	26		17%
Arrhythmia, total cases 36, 24%			
Auricular fibrillation	21		14%
Auricular flutter	2		2%
Arrhythmia, extrasystoles,	7		
Arrhythmia, unclassified (no electrocardiogram)	6		
Rheumatic heart disease, mitral (presys. or diast.)	6		
Other abnormal signs			
First sound at apex, poor quality,	4		
Rough first sound	3		
Slapping sounds	3		
Systolic shock	3		
Artery sounds increased	3		
Thrills, systolic and presystolic	3		
Tic tac	1		
Booming sounds	1		
P_2 accentuated	27		18%
Edema	11		7%
Liver enlarged	5		
Cyanosis	3		

Perhaps the greatest surprise was the infrequency of arrhythmia. This was noted in but 33 cases (22 per cent); of these there were 18 (12 per cent) of auricular fibrillation, 2 (2 per cent) of auricular flutter, and 7 (5 per cent) premature contractions. In 6 the disturbance was unclassified (no electrocardiogram.) Other less frequently encountered signs, occurring independently or in association with one or more of the previously discussed signs, are presented with their frequency of

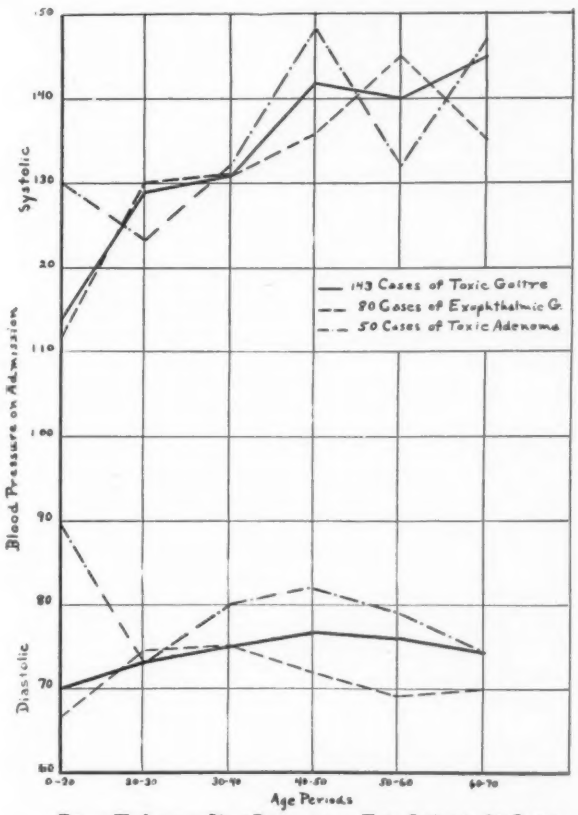

Figure IX—Average Blood Pressures in Toxic Goitre, by Age Periods

Number of Cases at each Age Period:							Total
T.G.	7	26	34	41	25	10	143
E.G.	6	30	25	19	10	2	80
T.A.	1	4	5	20	13	7	50

incidence in Table III. Excluding tachycardia, the heart was found entirely normal by every means of examination employed in the individual case in 34 patients (23 per cent). In some cases this was determined only by the usual means of physical examination, in some by x-ray and the electrocardiogram.

Signs of decompensation occurred in only 19 (13 per cent) cases; in these there was dependent edema in 11 (7 per cent), the liver was enlarged in 5 (3 per cent), and there was cyanosis in 3 (2 per cent). The

TABLE IV

HEART SIGNS AND SYMPTOMS BY DECADES AND ACCORDING TO THE DURATION OF SYMPTOMS

	UP TO 20		20-30		30-40		40-50		50-60		60-70		TOTAL	TOTAL
	SIGNS	SYMP.	SIGNS	SYMP.	SIGNS	SYMP.	SIGNS	SYMP.	SIGNS	SYMP.	SIGNS	SYMP.	SIGNS	SYMP.
0 to 3 mo.	1	1	1	2	3	4	6	6	2	2			13	15
3 to 6 mo.		1	2	2	1	1	1	1					4	5
6 to 9 mo.			2	2	3	3	4	4	3	4			12	13
9 to 12 mo.	2	2	5	5	4	5	11	10	2	2	2	2	26	26
2nd year	1	1	4	4	4	5	6	6	3	3	1		19	19
3rd year	1	2	2	3		1			5	5			8	11
4th year				2			2	2	2	2			4	6
5th year						1					4	2	4	3
5th-10th year			2	1	2	2	1	1	1				6	4
10 years and more			2	2	1	4	5	6		1		1	8	14
Duration not determinable							1	1	1	1			2	2
Total	5	7	20	23	18	26	37	37	19	20	7	5	106	118
Auricular fibrillation					2		10		5		4		21 cases	
Congestive heart failure			4		2		5		6		2		18 cases	
Heart signs persisting after thyroidectomy			1		1		6		3				11 cases	

Criteria: Signs—more than tachycardia alone; e. g., heart enlarged, murmurs, B. P. +, edema, EKG abnormal, etc.
Symptoms—more than tachycardia; e. g., dyspnea, pain, palpitation, etc.

pulmonary second sound was accentuated in 27 (18 per cent). Whether this is indicative of anything more than the toxic effect on the heart, or whether it is an indication of early decompensation is a matter for debate.

Period in Thyrotoxicosis at Which Heart Signs and Symptoms First Appear.—Reference to Table IV shows how frequently both signs and symptoms of heart involvement occur in the early months of thyroid intoxication. Examination of Fig. I shows that this appears to be about proportional to the age distribution of our cases.

Pulse.—An attempt to study the pulse and blood pressure records of these cases indicated the need of determining the relative age incidence of the cases of exophthalmic goiter and toxic adenoma in this series. Fig. II shows that in the first group of cases the peak is reached in the fourth decade, while in the second group it is reached in the fifth decade, a finding entirely in accord with previous observations.

Employing the same method of study, it is found by reference to Fig. III that, if we compare the pulse records between the ages of twenty and sixty years, the pulse rates in exophthalmic goiter are considerably higher in the third and fourth decades than in toxic adenoma, that the curves cross in the fifth decade, the toxic adenoma cases showing a higher rate than the exophthalmic cases, and that the curves again cross in the sixth decade, the adenoma cases showing a steady decline in pulse rate. Our series presented only two cases of exophthalmic goiter in this decade, one a fibrillator with a rate of 170, the other with a regular rate of 90.

A similar comparison of the systolic and diastolic blood pressure of exophthalmic and toxic adenoma cases shows (see Fig. IV) that the systolic pressures in these two types, while fairly parallel, are inconstant. The diastolic pressure curves show a slight but constant elevation in the adenoma group.

Electrocardiogram.—An electrocardiogram was made in 62 cases of our series. Slurring of the R-wave was noted in 46 instances, and the most striking deviation from the normal was the occurrence of slurring in all three leads in 18 cases (29 per cent of the curves). Axis deviation occurred in 24 cases, to the right in 7 and to the left in 17 cases. The type and frequency of arrhythmias have been discussed earlier in this paper. Notching of the P-wave occurred in 25 cases (40 per cent of the curves). It was observed in all leads but notably in Leads II and III.

Antecedent Rheumatic Infection.—It was found that definite signs of rheumatic carditis occurred in 6 of the 148 cases of toxic goiter. This finding invalidates to this extent the notation of heart findings as a part of the thyroid heart picture.

This study emphasizes the desirability of the adoption of the standards of the American Heart Association by the various hospitals where there is any hope for the utilization of records for later statistical and clinical study.

DISCUSSION

Criteria.—We have excluded tachycardia as evidence of involvement of the heart other than as evidence of increased demands. We feel that the remaining criteria, some of which admittedly are at times noted in conditions where there is no evidence of heart involvement, in general are accepted as evidence of heart disturbance at least of a functional type. In a preliminary grouping of toxic and non-toxic goiter in a series of 196 cases we excluded many cases from the toxic group because there appeared to be some question as to true thyroid toxicity; therefore we believe this presentation of heart signs and symptoms in toxic goiter is accurate within the limitations of the number of cases presented.

Detailed Discussion of Symptoms of Heart Involvement in Toxic Goiter.—Dyspnea occurred slightly in excess of any other symptom (56 per cent). We were surprised to note that this symptom was complained of more frequently than tachycardia or palpitation.

Palpitation ranked next in frequency (53 per cent). Numerous authors have emphasized the importance of this symptom. Kerr and Hensel[1] believe that this very often represents a transient auricular fibrillation or flutter.

Dependent edema was complained of in 25 per cent and noted on examination in 7 per cent of our cases. Willius, Boothby and Wilson[2] noted this in one-fifth of their cases. This was the only symptom noted which was especially associated with congestive heart failure and it is of interest that 25 per cent of our cases, which we considered had symptoms and signs of heart disease, complained of swelling of the legs or feet.

Precordial or substernal pain was noted by 12 per cent. Dameshek[3] records this in 13.5 per cent of his series of 141 cases. The frequency of precordial pain in neurotic states and the recognized effect of the thyroid toxin on the nervous system renders this as a sole symptom of heart disease of very doubtful value; however, no cases included failed to show some other symptom of heart disease. In an undetermined number of the older patients cardiosclerosis may have been a factor, although we have no electrocardiographic evidence on this point. Certainly pain cannot be considered a common symptom in thyrotoxicosis.

Vertigo was complained of in 7 per cent of the cases, and an additional 3 cases complained of fainting attacks. Since the average age of the patients experiencing vertigo was 39 years, this can hardly be attributed to arteriosclerosis. The average systolic blood pressure in this group (vertigo cases) was 134 mm., the average diastolic was 79, and the average pulse pressure was 55, which would seem to indicate that some factor other than cardiac was the basis of vertigo in these cases. We suggest vasomotor instability associated with thyrotoxicosis as a more probable explanation.

Cardiac irregularity was complained of by 3 per cent of the patients, although it was noted in 22 per cent. In view of the recognized neurotic

tendency of these patients it is interesting that this striking symptom was not more frequently mentioned by the patient.

Heart consciousness was spoken of by only 4 patients in addition to the 18 who complained of pain, a point of interest as noted in the preceding paragraph in connection with cardiac irregularity in this type of patient.

We noted symptoms of heart disease in 118 of the 148 included cases, whereas *signs* were noted in only 106 of these. Willius[2] and his associates state: "The most outstanding fact is the infrequency in both types (exophthalmic and adenoma) of symptoms indicating the heart." No doubt their criteria were more rigid than ours. Kerr and Hensel[1] noted more or less marked cardiovascular symptoms in 44 per cent of 181 goiter patients, but of their cases approximately 50 per cent of the adenomas were considered non-toxic, reducing thereby their toxic series to about 148 cases, in other words, a group numerically similar to ours. Their figure of 44 per cent of cases showing cardiovascular symptoms should then be corrected to 65 per cent of the toxic cases in comparison with our figure of 79 per cent.

We were unable to note any difference in the symptoms in the two types, but such difference as seems to exist appeared to depend upon the age of the patient, duration of symptoms and the condition of the heart at the moment of the onset of the toxic insult.

We considered a heart normal if there were no physical, x-ray or electrocardiographic signs of abnormality other than tachycardia. Dameshek[3] has employed less rigid criteria for the normal heart in that he has considered a blowing systolic murmur (no note as to transmission) as a normal heart finding. With our standard we found 23 per cent in which there are no signs of heart abnormality.

Our standard for a normal pulse rate, 70 to 90, may be criticized; but it should be noted that all of these patients were residing at the time of observation at an altitude of one mile above sea level, where an increase in heart rate of at least ten beats per minute as compared to sea-level standards is considered well within normal, and rates of 85 to 90 are so frequently encountered in the normal individual that it seemed wise to establish this wide range of 70 to 90 per minute.

We feel that we do not possess satisfactory evidence regarding the duration of toxic symptoms in relation to heart enlargement, but we show that demonstrable heart enlargement occurred in 30 per cent of our cases and notably at the later ages in which thyrotoxicosis occurs (see Fig. I). A study of Figs. I and II suggests that toxic adenoma bears a greater causal relationship to enlargement than does exophthalmic goiter.

We made a study of enlargement in reference to the duration of symptoms, existing murmurs, etc., in an attempt to learn in what proportion of the cases enlargement was probably due to hypertrophy and what

proportion due to dilatation, but we were unable to arrive at any conclusion. We found enlargement without electrocardiographic evidence of myocardial damage, a point previously noted by McEachern and Rake.[4]

We noted apical systolic murmurs (40 per cent) much less frequently than shown by Dameshek,[3] who stated that only 10 to 15 per cent failed to show a loud, blowing systolic murmur. Willius[2] and his co-workers noted murmurs in nearly one-half of their cases. Excluding 6 cases of probable preexistent rheumatic endocarditis, we had 18 cases or 12 per cent in which the apical systolic murmur was found to be transmitted. Willius,[2] et al., classed these apical murmurs with a variable transmission as probably dilatation murmurs, a view with which we agree in the majority of cases.

Signs of congestive heart failure were noted in 13 per cent and in both exophthalmic goiter and toxic adenoma. Four cases occurred in the absence of auricular fibrillation.

Our records do not corroborate former statements as to blood pressure in goiter. Willius,[2] et al., stated that in exophthalmic goiter the pulse pressure is increased. We did not find this to be the case in the early decades; but there is this tendency in the later decades, although even at that period it is not striking. In adenoma the average diastolic pressure reaches a peak at between forty and fifty years, which is also the peak of the age incidence in our series; and at the same period the highest average systolic pressures are recorded. We do not feel that we are justified in making any general statement as to blood pressure in toxic goiter, other than that in toxic adenoma there does appear to be a substantial increase in the diastolic pressure.

Other Abnormal Signs.—A variety of signs frequently noted in connection with cardiovascular changes associated with thyrotoxicosis are listed in Table III. Rough and impure first heart sounds might well have been described by some other observer as systolic or presystolic murmurs, a fact to be borne in mind in the differentiation of mitral stenosis and the hyperthyroid heart. So far as we could ascertain, none of these presented other evidence, historical or physical, of rheumatic heart disease. The slapping and booming sounds and systolic shock together with increased artery sounds all denote an overactive heart and form part of the clinical picture of hyperthyroidism, but whether they indicate more than simple overactivity remains to be proven. Smith and Colvin[5] incline to the view that these sounds are indicative of hypertrophy when noted in the absence of definite signs of aortic insufficiency. It is possible that some of the 6 cases, which we grouped as rheumatic heart disease associated with toxic goiter, may have been instances of marked vascular phenomena of hyperthyroidism.

Arrhythmias.—Next to persistent tachycardia the most striking heart sign in toxic goiter is the evidence of auricular fibrillation. Certain

authors state that this is a purely functional condition—a statement difficult to disprove in certain instances, but its frequency in toxic goiter (our series 14 per cent; White[6] about 20 per cent) strongly suggests a profound, though possibly transient, change in the heart muscle.

The Electrocardiogram in Toxic Goiter.—In only a few instances were later or post-operative curves made; hence we have no means of determining whether the changes noted were transient or permanent.

While R-wave slurring near the base line may occur in normal tracings, it is generally accepted that slurring of the R-wave in all leads is never normal, and we found 29 per cent of the curves presenting this abnormality. Left axis deviation in 27 per cent of the curves is probably explained by the long continued cardiac overload maintained by these cases. Right axis deviation was noted in 7 cases. Pardee[7] considers this is a proof of mitral stenosis. Six of our goiter cases also presented clinical evidence of mitral stenosis.

Smith and Colvin[5] in a series of 100 hyperthyroid cases found a definite increase in the P-wave. With this observation we do not agree. We noted notching of the P-wave in 40 per cent of our curves. This is an incidence only slightly higher than that noted by Pardee, who stated that about one third of normal cases will show this change. A study of a larger series would seem desirable.

Several authors have noted T-wave changes, notably increased amplitude, which they considered specific. Our curves do not substantiate this. We have not noted increased amplitude of the R-wave as reported by certain authors.

We found definite electrocardiographic evidence of myocardial change, in addition to the disturbances in rhythm in a sufficient number of cases to warrant the conclusion that myocardial damage does occur in toxic goiter. We did not find any electrocardiographic sign or signs which we consider specific in toxic goiter.

SUMMARY

We have shown that about one third of our cases had enlargement of the heart at the time of examination; in some of these we have reason to believe this was persistent, but are unable to present figures on this point. We found apical murmurs in two-fifths of the cases. Since some apical murmurs persisted after the clinical improvement of the patient, we concluded that at least some of these were not due solely to cardiac dilatation.

A summary of all cases presenting signs of heart disturbance reveals that 106, or 71 per cent, showed some sign exclusive of tachycardia during the toxic state. In 11 cases (7 per cent) definite heart signs persisted after recovery following thyroidectomy. These observations lead us to conclude that at least temporary heart damage is present in approximately two thirds of the cases during the toxic stage and that in a

small group this damage is permanent. Others have presented theories and substantiating evidence as to the cause of this damage; but whether or not observers admit heart damage in toxic goiter, all agree that the cardiac manifestations occupy the center of the stage in the vast majority of the severe cases.

CONCLUSIONS

That the heart is gravely involved in the course of goiter intoxication is evident; that in the average case it is permanently damaged is neither proved nor disproved by these records. The fairly large number (46 per cent) of individuals in whom the condition after operation, with a resultant drop in the basal rate, is either not improved or is doubtful, and in whom the pulse rate remains somewhat elevated (above 90 in 33 cases) and dyspnea of some degree persists, strongly suggests that the heart has not fully recovered from the toxic insult; but nothing is presented in this study to prove the nature of this damage. It would seem that one is not dealing entirely with the "old heart" in these cases, but that at any age the toxins associated with goiter may so affect the heart as to cause some degree of permanent damage.

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(For discussion, see page 144.)

A CLINICAL STUDY OF GOITER IN THE PACIFIC NORTHWEST, WITH SPECIAL REFERENCE TO THE STATE OF THE HEART*

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FOR a number of years it has been known that endemic goiter prevails in the Pacific Northwest. From sporadic surveys[1] and from the results of the draft examinations it has been thought to be more frequent in this locality than in any other section of the United States. Surveys, however, conducted by the Public Health Service[2] would indicate that its incidence of goiter is less than that of Minnesota, in which region goiter finds its greatest frequency. The region of the Pacific Northwest embraces in general that part of the United States and Western Canada within and supplied more or less by the water sheds of the Cascade Mountains. It therefore includes Oregon, Washington and British Columbia and portions of Idaho and Montana. Utah and Wyoming also have a comparatively high incidence, and when added to that of the Cascade Mountain district, gives to the entire series an incidence varying between 10.01 and 27.00 per 1000 of population. A local survey among children of public school age in Oregon[2] revealed nodular goiter in 1.8 per cent of the boys and in 4.1 per cent of the girls. The cause of the high incidence of goiter in this region has been generally attributed, especially since the studies of McClendon and Hathaway,[3] to the low iodine content of the water which is used not only for drinking purposes but also for the irrigation of vegetable gardens and orchards. The water supply of the city of Portland, for instance, is from Bull Run Lake, of glacial origin, which lies at the foot of Mount Hood, and contains from 0.03 to 0.10 parts iodine per billion parts of water. In comparison the water of New York City contains 2.50 parts iodine per billion parts of water, and that of Stanford, California, 105.8 parts iodine per billion parts of water.

In the present paper we have analyzed a series of goiter patients studied and operated upon in the Portland Clinic during the years 1925, 1926 and 1927. Approximately 1500 patients with goiter were registered in the clinic during these years, of which number 1066 came to operation because of various surgical indications. Of the latter number 835 have been analyzed from the standpoint of the heart and the associated pathological structural changes in the thyroid because sufficiently accurate clinical data were noted in the histories to make such an analy-

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Read by Title.

sis possible. The majority of these cases belonged to the toxic nodular and the varying mixtures of the hyperplastic groups. Some nodular enlargements with normal basal metabolic rate and normal heart action were removed because of pressure symptoms and for cosmetic reasons. The patients themselves, with few exceptions, came from diverse places within the Cascade Mountain district and represent quite accurately therefore the types of goiter with symptoms found in this locality.

In the analysis of the patients an attempt has been made to obtain a reasonably accurate idea of the presence or absence of cardiac enlargement, of cardiac failure, and of auricular fibrillation in relation to age incidence, hypertension, basal metabolic rates, associated cardiopathies and the type of the goiter present. Cardiac enlargement was determined in some instances by orthodiagraphic measurement before the fluoroscope or from the seven-foot plate. Both methods are relatively inaccurate; their results do not check well on repetition. Many more instances were determined by percussion measurements on the chest wall and the location and character of the maximal thrust of the apex of the heart alone. The latter method is quite as satisfactory as the former. Cardiac failure before the beginning of congestive signs is oftentimes difficult to recognize. It undoubtedly existed many more times than are recorded in the tables. After dilatation of the right heart takes place and evidence of passive congestion is manifest, the most serious of the complications of thyrotoxicosis is present. Its significance depends, of course, upon the heart's response to preoperative treatment directed toward the failure, which, in turn, depends mainly upon the state of the myocardium and associated cardiac lesions, and not upon the duration or the degree of the failure itself. The character of the structural changes in the myocardium of the goiter patient suffering from thyrotoxicosis, and whether these changes are specific for the disease, is the problem of paramount importance which remains yet to be solved. It will not be determined by clinical studies, nor in all probability from human heart material. The presence of a related cardiac syphilis, a rheumatic heart lesion, or a cardiovascular hypertensive disease may influence the occurrence of fibrillation and of failure, but such diseases mask rather than clarify the question as to the cause of the peculiar toxic type of heart action which most clinicians of experience are agreed is not duplicated by other toxic agents. The problem must be solved, if ever, by animal experimentation and the reading into the human problem of those findings which seem to have a bearing upon the heart's action of the experimental animal.

For many years the classification of goiters has been made the subject of much study. For some time past we[4] have grouped the portions of glands removed at operation and the whole glands obtained at autopsy according to their gross pathological characteristics and predominating microscopic pathologic structures in a manner which agrees essentially

with the clinical classification now adopted by the American Association for the Study of Goiter. It is as follows:

I. Diffuse parenchymatous hyperplasia—marked increased activity.
   (1) Gross observations: Gland compact, vascular or ischemic, grayish to pinkish white and colloid-free.
   (2) Microscopic observations:
      (a) Hyperplasia and hypertrophy of epithelium.
      (b) Peripheral or general vacuolization of colloid.
      (c) Dilatation of lymph channels and engorgement of blood vessels.
      (d) Variable increase in the supporting stroma with or without round-cell infiltration.

II. Disseminated adenomatous hyperplasia—normal or moderately increased activity or no activity.
   (1) Gross observations: Gland diffusely reddish-brown without noticeable nodularity or accentuation of lobular markings; a variable amount of colloid and pinkish to yellowish gray opacities.
   (2) Microscopic observations:
      (a) Focal changes similar to those in group I.
      (b) Normal or colloid-distended alveoli.
      (c) Focal hyperplasia and hypertrophy of epithelium.
      (d) Interalveolar hillocks or intra-alveolar papillomatous projections.
      (e) Focal collections of round cells or pseudolymphnodes.
      (f) Focally increased vascularity and dilated lymph channels.
      (g) Focal fibrous increase of connective tissue.

III. Nodular adenomatous hyperplasia—subnormal, normal or moderately increased activity.
   (1) Gross observations: Variable nodular accentuation of the lobular markings with or without excessive storage of colloid cystic degeneration, hemorrhage, scarring or deposit of lime salt. The color usually varies with the regressive changes.
   (2) Microscopic observations:
      (a) Focal changes similar to those found in groups I and II and compensatory.
      (b) Characteristic retrogressive changes.
      (c) Areas of adenomatosis.

IV. Solitary adenoma.
   (1) Gross observations: Adenoma variable in size, circumscribed, solitary or multiple, grayish-white to dark reddish-brown, solid and cystic or colloid-filled. Regressive changes may be present.
   (2) Microscopic observations:
      (a) All stages of fetal types of alveoli.
      (b) Peripheral formation of pseudocapsule with round cell infiltration and compressed alveoli.
      (c) Focal hyperactive areas in adjoining parenchyma.
      (d) Adjacent areas of adenomatosis.

It will be observed in this grouping of thyroid diseases on the basis of the gross anatomical characteristics that the basic histological changes which bear evidence of increased secretion are essentially the same. That is to say, regardless of the gross alterations we recognize no specific disease entities of the thyroid. All hypersecretion is considered fundamentally one and the same process differing only as it is influenced by

extent, degree, age, other intercurrent diseases, and its effect upon other glands of internal secretion. The correlation of such a pathological anatomical grouping with the symptoms has been shown in a previous discussion.[5]

While the above outline permits a satisfactory pathological grouping of the various toxic goiters we meet, there are many instances seen in which several groups are represented in the structural picture of one gland from a pathological viewpoint and some others which clinically do not fit into the pathological group to which they are expected to belong. However, a certain degree of increased activity has been recognized in all of the glands belonging to the present series of cases, and, in a general way, it follows quite closely the degree of toxic heart action experienced by the patient. The heart action, incidentally, has been of more value in the recognition of mild thyrotoxicosis than all other symptoms.

For the clinical analysis of the cases in the series we follow, not the above pathological grouping, but a similar clinical classification, as follows:

1. Diffuse goiter (a) nontoxic (b) toxic. 2. Nodular goiter (a) nontoxic (b) toxic. We have also attempted to divide the diffuse toxic type of goiter according to the pathological picture into (a) diffuse parenchymatous goiter—true Graves' disease, and (b) diffuse adenomatous goiter. This distinction cannot be sharply drawn, for many glands of each group show both parenchymatous and adenomatous hyperplasia in varying degrees. Clinically, however, the cases are often distinct, for the one is more frequently seen in younger persons with acutely fulminating symptoms, whereas, in the other case the person is usually older —he has known of the presence of a goiter for a long time, and his thyrotoxic symptoms are less marked. Since the recognition of the use of iodine prophylactically and therapeutically, greater difficulty is encountered in separating these groups clinically and pathologically. It is now unusual for the pathologist to observe a thyroid gland with the characteristic findings of exophthalmic goiter.

In the table of general data (Table I) one notes, as has been observed by others before, that heart lesions in thyrotoxicosis appear most frequently in the middle and later decades of life. Its pathology is not an accepted entity; it may not be at all specific, although the occurrence of enlargement and auricular fibrillation in patients in the twenties may suggest a specificity. What have been considered to be specific lesions of the myocardium in experimental animals have been described by Goodpasture,[6] Cameron and Carmicheal,[7] Hashimoto,[8] and Takane.[9] Other investigators have denied significance to such findings. We have observed in experimental rabbits,[10] to which had been administered thyroid extract, thyroxin and desiccated gland substance from human hyperplastic glands, monocyte, plasma cell and eosinophile invasion, fat

TABLE I

RÉSUMÉ OF 835 CASES OF GOITER IN THE PACIFIC NORTHWEST WITH REFERENCE TO THE STATE OF THE HEART*

	MALES 148—PERCENTAGE 17.7: FEMALES 687—PERCENTAGE 82.3 AVERAGE AGE—MALES 45.5 (18 TO 74 YEARS): FEMALES 40.5 (14 TO 81 YEARS)						
	AVERAGE BLOOD PRESSURE	AVERAGE BASAL METABOLIC RATE	KNOWN DURATION OF GOITER	CARDIAC ENLARGEMENT AGE INCIDENCE	CARDIAC FAILURE AGE INCIDENCE	AURICULAR FIBRILLATION AGE INCIDENCE	KNOWN ASSOCIATED CARDIOPATHIES
Group 1 a. Nontoxic Nodular 109 Cases	136 81	+5	12 years	12 = 11% 20-29 = 0 30-39 = 1 40-49 = 2 50-59 = 5 60-69 = 3 70-79 = 1	0	0	Sclerosis 7 Cardio-renal 4
b. Toxic Nodular 359 Cases	148 81	+32	13 years	93 = 25% 20-29 = 3 30-39 = 14 40-49 = 16 50-59 = 35 60-69 = 19 70-79 = 6	20 = 5.5% 40-49 = 1 50-59 = 13 60-69 = 5 70-79 = 1	18 = 5.0% 40-49 = 3 50-59 = 9 60-69 = 6	Sclerosis 26 Cardio-renal 50 Rheumatism 2 Syphilis 2
Group 2 a. Nontoxic Diffuse 31 Cases	140 81	+1	6 years	2 = 6.4% 50-59 = 1 60-69 = 1	0	0	Sclerosis 2
b. Toxic Diffuse 328 Cases	143 79	+39	3⅔ years	115 = 35.1% 20-29 = 15 30-39 = 35 40-49 = 36 50-59 = 17 60-69 = 11 70-79 = 1	26 = 7.9% 20-29 = 3 30-39 = 7 40-49 = 7 50-59 = 6 60-69 = 3	21 = 6.4% 20-29 = 3 30-39 = 2 40-49 = 5 50-59 = 10 60-69 = 1	Sclerosis 20 Cardio-renal 14 Rheumatism 6 Syphilis 1

*The series includes 8 cases of carcinoma of the thyroid—1.2 per cent.

vacuole formation, moderate fibroblast increase and fraying of the muscle bundles. The control animals did not show these changes. The same lesions, including the fraying of the muscle fibers, were also observed in one rabbit which lived for six days after a bilateral sectioning of the depressor nerves and the destroying of the carotid sinus investments. A continuous tachycardia was produced by this procedure and thyroid substances were not administered. This single observation—it is difficult to keep such animals alive after such a surgical procedure—suggests the possibility that the change in the structure of the heart muscle is a traumatic and inanition effect due to the heart's racing. Considered in this light the long continued tachycardia of thyrotoxicosis may have a like effect, in which case the lesion should be considered clinically quite as much an entity as though produced by toxemia. The effect of advancing age is seen, also, in cardiac syphilis, in cardiorenal disease and chronic atherosclerosis, and failure occurs in them most frequently during the middle decades of life. The age element does not argue against the specific nature of these diseases. The association of other heart lesions is seen many times, particularly sclerosis and chronic hypertension, and the addition of this new factor may have added merely a greater load to the heart and another character, which can be recognized as more or less distinct from the underlying thyroid heart disease. Such associated factors undoubtedly hasten cardiac failure and make the ultimate recovery of the heart after thyroidectomy more problematical. Again, auricular fibrillation, paroxysmal and persistent, is seen more frequently in thyrotoxicosis than in any other form of heart disease. So significant is its presence in a person under fifty that the diagnosis of toxic goiter is at once considered probable. The suggestive evidence, in like manner, of the peculiar, quick, forceful thrust of the heart's beat, never seen in other heart diseases, leads one to the same conclusion. Three times in our experience has this type of heart action led to the exploration of the neck in patients in whom no palpable evidence of goiter could be recognized, and in each instance a small adenoma with hyperplasia was found.

Auricular fibrillation occurred in this series of cases 39 times or 4.7 per cent, a much smaller percentage than reported by Parkinson and Cookson[11] (27 per cent in 130 cases). The reason for this variance lies in the material studied. In any region in which goiter is endemic the inhabitants become goiter minded and seek surgical relief early. For this reason the majority of our patients were seen and operated upon before serious cardiac complications had developed. During the years embraced in the series; namely, 1925, 1926 and 1927, we were more cautious about the use of quinidine than we later became and the patients were not then treated as we treat them now. At that time we insisted upon a month or more passing after the operation before quinidine therapy was attempted. In the meantime many patients had

TABLE II

AURICULAR FIBRILLATION IN TOXIC DIFFUSE GOITER, DIFFUSE ADENOMATOUS TYPE, 10 CASES

						END-RESULTS					
						RELIEVED BY					
AGE	SEX	TYPE OF HEART PATHOLOGY	BLOOD PRESSURE	DURATION	NOT TREATED	OPERATION	STROPHANTHIN DIGITALIS	QUINIDINE SULPHATE	RELAPSED	PERMANENT	REMARKS
37	F	Thyroid	190/100	5 months	+	+	–	–	–	–	–
48	M	Thyroid	140/85	7 months	+	–	–	–	–	+	–
59	F	Sclerosis Thyroid	170/100	4 months	+	+	–	–	–	–	–
62	M	Sclerosis Thyroid	136/70	6 months	+	Followed operation by several months	–	–	–	+	–
53	F	Sclerosis Thyroid	200/95	1 month	+	+ Paroxysmal	–	–	–	–	–
23	F	Thyroid	130/80	1 year	+	+ Paroxysmal	–	–	–	–	–
40	F	Thyroid	140/70	1-2 years	+	+ Paroxysmal	–	–	+	–	–
55	F	Sclerosis Thyroid	190/110	2 years	+	–	–	–	–	+	–
56	F	Sclerosis Thyroid	216/90	–	+	Followed operation	Digitalis 5 gr.	–	–	–	–
52	F	Sclerosis Thyroid	185/80	3 months	+	+	–	–	–	–	–

returned to distant homes and as their health was much improved in spite of the associated fibrillation they were never treated for it. In the more recent years such patients have been more systematically treated with quinidine and in about 85 per cent of them normal sinus rhythm has been restored. However, in spite of the absence of proper treatment, one notes certain suggestive points of difference among the cases of the three toxic groups outlined in Tables II, III, and IV. Auricular fibrillation in the diffuse parenchymatous or Graves' disease group tends to persist unless sinus rhythm is restored by means of quinidine. In the diffuse adenomatous type, however, restoration of sinus rhythm followed operation alone 6 times in 10 cases. In the toxic nodular group it has existed usually for a longer period of time when the patient is first seen; it is apt to be more persistent and, if broken by quinidine, it is quite apt to relapse. Again, that fibrillation from thyrotoxicosis is not dependent upon degenerative changes of advancing years is suggested by its presence 5 times under the age of forty and 3 times under the age of thirty without the association of other heart diseases. That fibrillation and cardiac enlargement or congestive failure as well may exist at the age of 23, 25 or 29 without the aid of other cardiac disease is of much greater significance than the fact that they occur more frequently at an age when syphilis, cardiorenal hypertensive disease and the cardiosclerosis are taking their greatest toll.

TREATMENT

The treatment of the goiter patient with thyroid heart disease has become, in our hands, more or less standardized. The patient, with or without auricular fibrillation, but without cardiac failure, is placed at bed rest for several days before operation. His diet contains from 45 to 55 grams of protein, from 1 to 2 grams of salt, calories as desired, and a fluid intake of 1000 to 1500 c.c. per day. Deodorized tincture of opium, minims 10, in capsules, is given from 2 to 6 times per day until he rests quietly. Opium given in this manner affords much comfort to the patient suffering from either form of toxic goiter and the heart's action quiets rapidly under its influence. Iodine as a rule is given only to patients suffering from Graves' disease. Usually 5 minims of Lugol's solution three times per day for a few days before operation is sufficient to control the toxemia, but in the presence of a severe crisis it is given in large doses intravenously as sodium iodide, Lugol's solution by rectum and later by mouth until the acute thyrotoxic symptoms have subsided. After operation Lugol's solution, 5 minims a day, is often continued in these cases for 4 to 6 weeks. No special therapy is prescribed. The patient is directed not to exert himself to the point of shortness of breath for six months.

In the presence of cardiac failure the problem is different. An attempt to restore compensation is made before operation is performed.

TABLE III

AURICULAR FIBRILLATION IN TOXIC DIFFUSE GOITER, PARENCHYMATOUS TYPE, 11 CASES

AGE	SEX	TYPE OF HEART PATHOLOGY	BLOOD PRESSURE	DURATION	NOT TREATED	END-RESULTS					
						RELIEVED BY			RELAPSED	PERMANENT	REMARKS
						OPERATION	STROPHANTHIN DIGITALIS	QUINIDINE SULPHATE			
25	F	Thyroid	140/70	2 years	+	–	–	–	–	+	–
38	F	Thyroid	140/80	5 months	+	–	–	–	-	+	–
55	M	Thyroid	140/80	6 months	+	+	–	–	–	–	–
29	F	Thyroid	150/90	6 months	+	+	–	–	–	–	–
40	F	Thyroid	122/78	5 months	+	–	–	–	–	+	–
42	F	Thyroid	160/80	6 months	+	–	–	–	–	+	–
44	F	Thyroid	158/90	10 years	+	–	–	–	–	+	–
37	M	Thyroid	120	6 months	+	–	–	–	–	+	–
54	F	Thyroid		5 years	+	–	–	–	–	+	Died before operation
55	M	Sclerosis Thyroid	185/85	2 years	–	Followed operation	–	48 grains 21 grains 6 grains	+		Died 1 year later. Cerebral hemorrhage
50	F	Thyroid	140/80	2 years	+	–	–	–	–	+	–

TABLE IV

TOXIC NODULAR GOITER, 18 CASES

AGE	SEX	TYPE OF HEART PATHOLOGY	BLOOD PRESSURE	DURATION	NOT TREATED	END-RESULTS: RELIEVED BY: OPERATION	RELIEVED BY: STROPHANTHIN DIGITALIS	RELIEVED BY: QUINIDINE SULPHATE	RELAPSED	PERMANENT	REMARKS
61	F	Sclerosis Thyroid		Paroxysmal	+	–	–	–	–	–	Died before operation
56	F	Thyroid	105/60	Paroxysmal	–	–	Digitalis	–	+	–	–
52	F	Thyroid	156/90	?	–	–	–	61 grains	–	–	–
55	F	Thyroid	180/90	?	+	–	–	–	–	+	–
62	F	Sclerosis Thyroid	120/80	?	+	–	–	–	–	+	–
53	F	Sclerosis Thyroid	166/92	?	–	–	–	Quinidine	+	–	–
41	M	Thyroid	170/80	?	+	–	–	–	–	+	–
52	F	Sclerosis Thyroid	220/120	?	+	–	–	–	–	+	–
58	F	Sclerosis Thyroid	190/90	Paroxysmal	–	–	Strophanthin	–	–	–	Precipitated by operation

TABLE IV CONTINUED

					END-RESULTS						
						RELIEVED BY					
AGE	SEX	TYPE OF HEART PATHOLOGY	BLOOD PRESSURE	DURATION	NOT TREATED	OPERATION	STRO-PHANTHIN DIGITALIS	QUINIDINE SULPHATE	RELAPSED	PERMA-NENT	REMARKS
62	F	Sclerosis Thyroid	160/90	?	+	–	–	–	–	+	–
60	F	Sclerosis Thyroid	250/120	?	+	–	–	–	–	+	–
53	F	Sclerosis Thyroid	165/90	?	+	–	–	–	–	+	–
48	F	Thyroid	170/75	?	+	–	–	–	–	+	–
59	F	Sclerosis Thyroid	145/80	?	–	–	–	–	–	+	Began 3 years after operation 126 grains Quinidine—no result
63	F	Sclerosis Thyroid	170/80	10 years ago relieved by operation 5 months	+	–	–	–	–	+	
50	F	Sclerosis Thyroid	165/90	4 years	+	–	–	–	–	+	–
46	F	Thyroid	170/85	1 year	+	–	–	–	–	+	–
52	F	Sclerosis Thyroid	180/90	9 months	+	–	–	–	–	+	–

In a limited number of cases it has been impossible to overcome the failure, and, after careful consideration of each case, thyroidectomy has been done in its presence. This course has been followed in only a few instances, and fortunately, thus far, without an immediate operative death. With the presence of general edema treatment is often started with a Karell milk diet, and after two days of its use the diet is changed to the above low protein, low salt diet, and the liquid intake restricted to 800 c.c. or less per day. The Minnesota grown powdered digitalis leaves are administered, 4 grains per day, until physiological tolerance is reached. Complete digitalization is usually obtained in three to five days. At times strophanthin, gr. 1/500 (B. & W.) intravenously administered, and repeated in two hours, is used at the beginning of treatment. This is given particularly in the presence of severe congestive symptoms and rapid fibrillation. Salyrgan is a valuable adjunct in the removal of fluid from the body. After compensation is restored and the patient has become quiet, all digitalis is stopped for a period of three or four days—following the idea of Plummer that the operative risk is less after the patient is out from under its influence. We have no evidence to substantiate this idea. After operation a long period of control of the heart is enjoined upon the patient. He is urged

TABLE V

RÉSUMÉ OF AURICULAR FIBRILLATION IN DIFFUSE AND NODULAR GOITER

Group I.—

1. Diffuse goiter, toxic
   (a) Diffuse parenchymatous (exophthalmic) 11 cases
   Average age 42.6 years (25 to 55 years)
   Sex: Male 3, Female 8
   Cardiac pathology: Thyroid heart 11, with cardiosclerosis 1
   Average blood pressure: Systolic 145.5 millimeters of mercury
   Diastolic 81.4 millimeters of mercury
   Duration: usually a few months
   End-result: usually permanent unless treated with quinidine
   (b) Diffuse adenomatous (disseminated or spotty parenchymatous)
   Goiter: 10 cases
   Average age 48.5 years (23-62 years)
   Sex: Male 2, Female 8
   Cardiac pathology: Thyroid heart 10 Cardiosclerosis 6
   Average blood pressure: Systolic 170 millimeters of mercury
   Diastolic 88 millimeters of mercury
   Duration: usually few months
   End-result: sinus rhythm seemingly more easily restored
2. Diffuse goiter, nontoxic, no cases

Group II.—

1. Nodular Goiter, toxic, 18 cases
   Average age 54.5 years (41 to 63 years)
   Sex: Male 1, Female 17
   Cardiac pathology: Thyroid heart 18 Cardiosclerosis 12
   Average blood pressure: Systolic 145.5 millimeters of mercury
   Diastolic 84.4 millimeters of mercury
   Duration: usually long continued
   End-result: usually permanent or relapsing
2. Nodular goiter: nontoxic, no cases

to live quietly without exertion for a period of a year. Many times this advice is not followed. Sometimes the patient returns after a few weeks or months again in failure and it is then that recompensation is obtained with the greatest difficulty; in fact many times it is not obtained. The favorable prognosis for failure seen before and with thyroidectomy becomes the gloomy prognosis of failure seen in the syphilitic and the cardiorenal heart. Associated heart lesions often play a role in the return of failure, but in some of our patients they have not played such a role.

The frequent presence of auricular fibrillation in thyroid heart disease adds an interesting phase to the treatment of the thyrotoxic patient. Formerly when quinidine sulphate was used with considerable apprehension the patient with persistent fibrillation was directed to return from 4 to 6 weeks after operation for its administration. As experience in its use was gained, however, we gave it to patients with less and less delay, until for the past two years we have given an initial test dose of 3 grains on the third and fourth days after operation. Then, without untoward symptoms appearing, we have administered 3, 6 and 9 grains per dose three times per day until sinus rhythm was restored or failed to be obtained. No two patients respond alike. Amounts of quinidine administered have ranged from the initial dose of 3 grains to 500 grains during one period of treatment. One or two grains per day are often prescribed for a week or longer after normal sinus rhythm has been resumed, in the hope of preventing recurrence of fibrillation. Should recurrence take place quinidine is again given. Thus far we have seen no accidents attend its use, and we have learned to look upon the procedure as safe when carried out under control. When auricular fibrillation remains persistent it is often necessary to control it by suitable tonic doses of digitalis, for fibrillation occurring with the thyroid heart tends to be of rapid rate and cause symptoms of embarrassed heart action by reason of its rapidity.

SUMMARY

Eight hundred and thirty-five goiter cases from the Pacific Northwest states are analyzed, chiefly from the standpoint of cardiac enlargement, cardiac failure, and auricular fibrillation in relation to age incidence, basal metabolism, arterial hypertension, associated cardiopathies and the type of the goiter present.

Although cardiac failure and auricular fibrillation are seen usually as an accompaniment of advancing years, it is pointed out that they occur also before the age of thirty in goiter patients in whom other heart diseases are absent. This fact, together with the characteristic thyrogenic heart action and certain experimental evidence, suggests the probability of specific thyroid heart lesions.

The general plan of treating heart complications in thyrotoxicosis in the clinic is outlined.

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CARDIOVASCULAR SYMPTOMATOLOGY IN EXOPHTHALMIC GOITER*

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IN THE past two and a half years the histories and physical examinations of patients coming to the Thyroid Clinic have been recorded on a special record sheet. This is designed to permit the use of modern mechanical methods to analyze the data. The method of recording the information, the transfer to punch cards, and its analysis by means of a sorting machine have been described elsewhere.[1] By the use of these methods, we have now available information on 619 patients with goiter seen from January, 1930, to February, 1932, inclusive. Those with a questionable diagnosis were excluded. The present study is based on an analysis of 184 cases of toxic goiter, using 233 cases of non-toxic nodular goiter as control. The toxic group contains cases of nodular goiter with hyperthyroidism as well as cases of exophthalmic goiter. The tables have been arranged to bring out differences in symptomatology in the two sexes occurring in hyperthyroidism. The control group, however, has not been subdivided because the 18 male patients belonging to this group are not sufficient for a control. Consequently the group of non-toxic nodular goiter is adequate as a control only for the female patients with hyperthyroidism.

TABLE I

AGE DISTRIBUTION OF 233 PATIENTS WITH NON-TOXIC NODULAR GOITER AND OF 184 PATIENTS WITH TOXIC GOITER

	NODULAR GOITER (NON-TOXIC)		HYPERTHYROIDISM			
			MALE		FEMALE	
AGE	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
-19	18	7.7	3	5.8	13	9.8
20-29	37	15.9	10	19.2	33	25.0
30-39	72	30.9	9	17.3	34	25.8
40-49	54	23.2	19	36.5	32	24.2
50-59	42	18.1	8	15.3	15	11.4
60-69	7	3.0	3	5.8	5	3.8
70+	3	1.3				
Total	233		52		132	

*From the Thyroid Clinic and Metabolism Laboratory of the Massachusetts General Hospital.

RESULTS

Table I gives the age distribution of patients with hyperthyroidism, 52 males and 132 females, and of 233 patients with non-toxic nodular goiter. It is seen that male hyperthyroid patients were older than females to some extent. Thus 25 per cent of the male patients belonged in the age group under thirty years and 21.1 per cent in the group of fifty years and over. The corresponding figures for female patients are 34.8 per cent and 15.2 per cent respectively. The ages of the non-toxic goiter group were about the same as those of the male hyperthyroid group.

TABLE II

THE BASAL METABOLIC RATE IN NON-TOXIC NODULAR GOITER AND IN HYPERTHYROIDISM

	NODULAR GOITER (NON-TOXIC)		HYPERTHYROIDISM			
			MALE		FEMALE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
-Minus 20	4	1.7				
Minus 19-Minus 10	29	12.5				
Minus 9-Minus 1	61	26.1				
0-Plus 14	114	48.9	2	3.8	7	5.3
Plus 15-Plus 29	25	10.7	6	11.5	34	26.0
Plus 30-Plus 44			22	42.3	49	37.4
Plus 45-Plus 59			10	19.2	28	21.4
Plus 60-Plus 74			10	19.2	9	6.9
Plus 75+			2	3.8	4	3.1

Table II shows the comparison of severity of hyperthyroidism as measured by the basal metabolic rate in male and female patients. On the whole, there were more severe cases among the males than among the females. Thus 23 per cent of the male patients had metabolic rates of plus 60 and over, whereas only 10 per cent of the female patients had this degree of metabolism.

In Table III the important cardiac symptoms are analyzed with respect to their frequency, severity and duration. In general all of the symptoms were more common in the female than in the male patients with hyperthyroidism, in spite of the fact that the male patients were older and more frequently had a severe form of the disease. The actual correction for age and basal metabolic rate makes a slight change only in the percentage figures. For example, the incidence of palpitation in male hyperthyroid patients changes from 77.0 to 75.3 per cent and for

females it changes from 91.7 to 92.6 per cent. It is interesting to note that the frequency of precordial pain in hyperthyroidism is not much greater than in the control group.

This table, in addition, shows that the severity of the cardiac complaints was greater in the hyperthyroid than in the non-toxic patients and that the symptoms were much milder in the male than in the female

TABLE III

THE INCIDENCE OF SOME IMPORTANT CARDIAC SYMPTOMS, AND OF THEIR SEVERITY AND DURATION IN NON-TOXIC NODULAR GOITER AND IN HYPERTHYROIDISM

	NODULAR GOITER (NON-TOXIC)		HYPERTHYROIDISM			
			MALE		FEMALE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Palpitation	119	51.1	40	77.0	121	91.7
Irregular heart	11	4.8	4	7.7	12	9.2
Dyspnea	115	49.6	39	75.0	117	88.6
Precordial pain	36	15.8	7	13.7	26	20.2
Average severity:						
Mild	107	73.8	26	55.3	42	33.3
Moderate	36	24.8	18	38.3	68	54.0
Severe	2	1.4	3	6.4	16	12.7
Duration:						
-1 month	1	0.7	2	4.3	2	1.6
1-4 months	13	9.0	10	21.3	25	19.8
4-12 months	19	13.1	15	31.9	36	28.6
1-2 years	27	18.6	12	25.5	15	11.9
2-5 years	35	24.1	4	8.5	34	27.0
5-10 years	18	12.4	1	2.1	6	4.8
10+ years	12	8.3	2	4.3	7	5.6
Unknown	20	13.8	1	2.1	1	0.8

patients. The duration of cardiac symptoms was longer in the non-toxic than in the toxic groups, and longer in the female than in the male group. For example, 20.7 per cent of the patients with non-toxic goiters had cardiac symptoms for 5 years or longer, whereas 10.4 per cent of the female and 6.4 per cent of the male patients with hyperthyroidism had symptoms of this duration. The percentage of patients having symp-

toms for less than 4 months was 9.7 per cent, 21.4 per cent and 25.6 per cent respectively.

Table IV shows the incidence of a variety of symptoms and signs dealing with the cardiovascular system or having some bearing on it. Several important facts may be deduced. Female hyperthyroid patients tended to be heavier than male patients; they had exophthalmos less

TABLE IV

THE INCIDENCE OF MISCELLANEOUS CARDIAC SYMPTOMS AND SIGNS IN NON-TOXIC NODULAR GOITER AND IN HYPERTHYROIDISM

	NODULAR GOITER (NON-TOXIC)		HYPERTHYROIDISM			
			MALE		FEMALE	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Increased heat loss*	60	25.9	45	86.6	116	87.8
Weakness	139	60.0	41	78.8	115	88.5
Obesity	45	19.3	-	-	7	5.3
Underweight	41	17.6	25	48.1	57	43.2
Exophthalmos	4	1.8	36	70.6	73	53.8
Cyanosis of lips	2	0.9	2	3.8	4	3.0
Pallor of lips	16	6.9	-	-	4	3.0
Thyroid:						
Normal	2	0.9	4	7.7	5	3.8
Slightly enlarged	147	63.1	35	67.3	83	62.9
Moderately enlarged	76	32.6	13	25.0	44	33.3
Greatly enlarged	8	3.4	-	-	-	-
Cardiac enlargement	23	9.9	15	28.9	55	42.3
Fibrillation	2	0.9	6	11.5	9	6.8
Other arrhythmias	6	2.6	3	5.8	5	3.8
Orthopnea	7	3.0	5	9.6	10	7.6
Precordial thrill	2	0.9	3	5.8	12	9.2
Valvular disease	3	1.3	1	2.0	4	3.1
Pericardial disturbance	-	-	3	5.9	15	11.8
Arteriosclerosis-peripheral	69	29.6	32	61.6	26	19.7
Cardiac disease	30	12.9	7	13.5	17	12.9
Cardiac disease without rheumatic heart disease	26	11.2	6	11.5	15	11.4

*Includes symptoms of increased sensation of heat and increased perspiration.

often, and their goiters tended to be larger. Cardiac enlargement, as measured by percussion, was more common in the female, whereas auricular fibrillation and other forms of arrhythmia were more common in the male. The cardiac enlargement is more often apparent than real, because the size of the heart, as obtained by percussion, is exaggerated by its overactivity and very often does not check with the measurements obtained by roentgen ray. A precordial thrill was felt more frequently in the female than in the male patient. Valvular disease occurred in the control to almost the same extent as in the hyperthyroid groups. Evidence of pericardial disturbance in the form of a friction rub, to be discussed below, was more common in the female. Of the above factors, cardiac enlargement, precordial thrill and pericardial friction rub are partly indicators of the degree of activity of the heart.

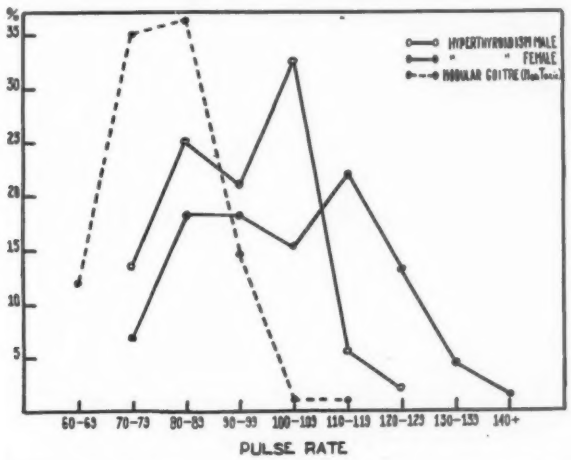

Fig. 1.—Distribution of the pulse rate in 51 male patients with hyperthyroidism, 131 female patients with hyperthyroidism and 233 patients with non-toxic nodular goiter.

It seems, therefore, that the heart was more overactive in the female than in the male hyperthyroid patient.

The incidence of peripheral arteriosclerosis in the female hyperthyroid group, namely 19.7 per cent, was to be expected on the basis of age distribution, using the control group of non-toxic nodular goiters for comparison. The incidence of peripheral arteriosclerosis in the male toxic goiter group was about three times that of the female group. Since the control group was composed mainly of female patients, it is impossible to say whether the high incidence of arteriosclerosis in the male group was abnormal or to be expected on the basis of age. It is possible that male patients have their disease for a much longer period of time than the results indicate, since notoriously they complain very little until late in the course. Consequently the changes in the vessels, resulting from long standing thyrotoxicosis may account for part of the large number with

arteriosclerosis. The incidence of organic cardiac disease was about the same in the three groups of patients, i. e., 13 per cent.

The relation of pulse rate to pulse pressure in hyperthyroidism showed interesting difference between the sexes. The pulse in male patients was slower than in female patients, as indicated in Fig. 1. For example, 38.5 per cent of the males showed pulse rates under 90, against 25.2 per cent of females, and 7.7 per cent of males showed pulse rates of 110 and over against 41.2 per cent of females. This difference in pulse rates existed in spite of the greater number of severe cases in the male group. In terms of averages and their standard deviations, this difference may be expressed $104.0 \pm 1.5 - 94.8 \pm 1.7$ or 9.2 ± 2.5, a value of high statistical significance. On the other hand the pulse pressure of the male group was larger than that of the female (Fig. 2). For example,

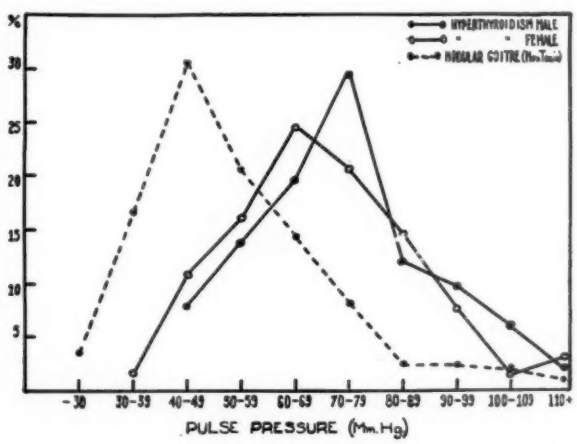

Fig. 2.—Distribution of the pulse pressure in 51 male patients with hyperthyroidism, 131 female patients with hyperthyroidism and 226 patients with non-toxic nodular goiter.

21.4 per cent of the male patients had pulse pressures under 60 mm. of Hg against 28.2 per cent of the female patients; 17.7 per cent of the male patients had pulse pressures of 90 mm. and over, against 12.2 per cent of the females. This difference as expressed by averages is $74.0 \pm 2.3 - 70.0 \pm 1.5$ or 4.0 ± 2.9, a value of probable significance, although not of the same order as in the case of the pulse rate because of the greater dispersion of readings. Since the pulse pressure is roughly an indication of the output of the heart per beat, it seems that the net result as far as the volume flow of blood is concerned was the same in the two groups. In the one the demands upon the circulation were largely met by increasing the heart rate and in the other by increasing the output per heart beat.

The attempt has been made to correlate the important cardiac symptoms of palpitation and dyspnea and their severity with some of the fac-

TABLE V

THE CORRELATION OF PALPITATION AND DYSPNEA IN HYPERTHYROIDISM AND THEIR SEVERITY WITH SOME RELATED FACTORS (PERCENTAGE FREQUENCY)

	PALPITATION	DYSPNEA	SEVERITY OF PALPITATION AND DYSPNEA		
			MILD	MODERATE	SEVERE
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Average Frequency	*87.5*	*84.8*	*39.3*	*49.7*	*11.0*
Obesity	100.0	100.0	14.4	85.6	-
Undernourishment	92.7	86.6	35.4	50.6	14.0
Size of thyroid:					
1. Normal	88.9	100.0	55.5	33.5	11.0
2. Slight enlargement	85.6	82.2	37.6	51.4	11.0
3. Moderate enlargement	91.2	87.7	40.0	49.2	10.8
Cardiac enlargement	95.7	87.2	21.7	59.4	18.9
Fibrillation	100.0	100.0	26.6	40.0	33.3
Other arrhythmias	100.0	87.5	25.0	75.0	-
Precordial thrill	100.0	93.3	20.0	66.7	13.3
Valvular disease	100.0	100.0	-	60.1	39.9
Pericardial disturbance	88.9	88.9	27.8	66.6	5.6
Arteriosclerosis-peripheral	86.2	82.8	45.5	43.6	10.9
Cardiac disease	95.8	95.8	23.8	47.6	28.6
Basal metabolic rate:					
Under 30	79.6	75.5	41.5	51.2	7.3
30-44	87.3	87.3	43.5	44.9	11.6
45+	93.6	88.9	33.9	54.8	11.3
Pulse rate:					
Under 100	84.1	84.1	48.8	41.5	9.7
100+	90.5	85.3	31.1	57.8	11.1
Pulse pressure:					
Under 80	83.3	84.1	41.8	48.4	9.8
80+	100.0	87.0	32.0	54.0	14.0

tors mentioned above. They are listed in Table V. The incidence of palpitation and dyspnea in all the hyperthyroid patients was 87.5 per cent and 84.8 per cent respectively, and of their severity 39.9 per cent, 49.7 per cent and 11.0 per cent for mild, moderate and severe degree respectively. Age did not affect the frequency of these two symptoms except for the small group of patients under 20 years for which the incidence was 62.5 per cent for each symptom. The severity did not show a consistent trend with age, but there was a slight tendency to greater severity in the older age groups. Both obesity and undernourishment were associated with a greater frequency of palpitation and dyspnea and a greater severity than usual. The size of the thyroid gland did not show a consistent relationship. There was a greater than average incidence of palpitation and dyspnea, as well as greater severity, in the groups of patients with cardiac enlargement, fibrillation, other arrhythmias, precordial thrill, valvular disease, other organic cardiac disease, and pericardial friction rub. On the other hand peripheral arteriosclerosis was not associated with such an increase. There was a direct correlation between the incidence of palpitation and dyspnea and their severity on the one hand, and the level of metabolism, pulse rate and pulse pressure on the other, with the exception of dyspnea in relation to the pulse rate. The relationship between the severity of symptoms and the metabolism was somewhat dubious. Some of the factors associated with a high incidence of palpitation and dyspnea and with greater than average severity were more frequent in the male, and some in the female. The variation was such that it is impossible to account on this basis for the greater frequency of palpitation and dyspnea in the female and also for the greater severity of these symptoms.

As indicated previously, there were 24 patients with organic cardiac disease associated with hyperthyroidism. Three of these had rheumatic heart disease. In Table VI is listed the incidence of various symptoms and signs in this group. All but one of these patients were 40 years of age or older. Compared to the group uncomplicated by cardiac disease, the incidence of palpitation and dyspnea was greater by about 10 per cent. There was more obesity, and the goiters tended to be smaller. Cardiac enlargement was present to the extent of 86 per cent, against 32 per cent for the uncomplicated group, fibrillation 57 per cent, against 1.8 per cent, other arrhythmias 14 per cent, against 3 per cent, and peripheral arteriosclerosis 71 per cent, against 27 per cent. Precordial thrill, valvular disease and pericardial disturbance were less common in the group with cardiac disease. Finally, the basal metabolic rate, the pulse rate and pulse pressure varied little from those of the uncomplicated group.

DISCUSSION

The supposition of a special toxic damage to the cardiovascular system in hyperthyroidism has been made by many. There is one im-

portant difference between the non-toxic and the toxic groups. In the former, cardiac disease took the form of hypertensive or arteriosclerotic heart disease in 20 of the 30 cases, auricular fibrillation in 1, paroxysmal tachycardia in 2, and angina in 1; in the latter, cardiac disease took the form of hypertensive and arteriosclerotic heart disease in 5 of the 24

TABLE VI

INCIDENCE OF CERTAIN SYMPTOMS AND SIGNS PRESENT IN 21 PATIENTS WITH CARDIAC DISEASE ASSOCIATED WITH HYPERTHYROIDISM COMPARED TO THAT SEEN IN UNCOMPLICATED CASES OF HYPERTHYROIDISM

	CARDIOVASCULAR GROUP		UNCOMPLICATED GROUP	
	NO.	PER CENT	NO.	PER CENT
Palpitation	20	95.2	141	86.5
Dyspnea	20	95.2	136	83.4
Obesity	2	9.5	5	3.1
Undernourishment	9	42.8	73	44.8
Size of thyroid:				
Normal	3	14.3	6	3.7
Slight enlargement	14	66.7	104	63.8
Moderate enlargement	4	19.1	53	32.5
Cardiac enlargement	18	85.7	52	32.3
Fibrillation	12	57.1	3	1.8
Other arrhythmias	3	14.3	5	3.1
Precordial thrill	1	4.8	14	8.6
Valvular disease	0	0	5	3.1
Pericardial disturbance	0	0	18	11.5
Arteriosclerosis-peripheral	15	71.4	43	26.8

cases, and of either auricular fibrillation, angina or congestive failure, singly and in combination, in 16 cases. It seems, therefore, that in the hyperthyroid group cardiovascular damage consists chiefly in a functional disturbance rather than a structural change. The fact that almost all these people were older than the hyperthyroid patients without cardiac disease, and the high incidence of peripheral arteriosclerosis suggest that hyperthyroidism *per se* is not responsible for the so-called thyroid heart disease, but produces functional disturbance in a previously damaged cardiovascular system. This surmise is supported by the fact that we often see patients who have had hyperthyroidism for ten years or more without any evidence of cardiac damage. It is, never-

theless, true that occasionally a young person with thyrotoxicosis develops cardiac failure without evidence of a previously damaged heart. The above findings are in agreement with the conclusions of Andrus.[2]

As mentioned earlier, we have noted an unusual systolic noise in the moderate and severe cases of hyperthyroidism. It consists of a rough, grating systolic murmur which has some of the characteristics of a friction rub, heard best over the sternum in the region of the second interspace. It is superficial, heard best at the end of full expiration and obscured by full inspiration. Its intensity subsides as the metabolism and heart rate drop under the influence of iodine and usually disappears after operation. On several occasions the diagnosis of pericarditis was suspected by members of the hospital staff on the basis of this friction rub. We are not certain as to its causation. The fact that it is superficial and disappears with inspiration has led us to believe that it is pleuro-pericardial in origin. It may have some relationship to the dilated pulmonary conus often seen in the roentgen ray pictures in this condition. In the above series a superficial friction rub was observed in 10 per cent of the patients, but this figure represents only the outspoken cases. The milder friction sounds were not recorded. At present no diagnostic or prognostic significance can be attached to it.

Some time after we became aware of the existence of this sign, we found that other observers had described it in the literature. Goodall[3] in 1920 noted a superficial pericardial rub in patients with hyperthyroidism, most common over the pulmonary area and often associated with a definite cardiac oppression or actual pain. He suggested that it was probably produced mechanically by a dilated heart. In 1927 Smith and Calvin[4] also described a systolic rubbing sound in the pulmonic area in 40 or 50 per cent of their patients. In some it was very intense; in others it seemed to roughen the systolic murmur already present in this area.

SUMMARY

An analysis of 184 patients with hyperthyroidism shows that cardiac symptoms are more common in the female; their severity is greater and their duration longer. Cardiac enlargement, precordial thrill and a superficial pericardial friction rub are more common in the female, whereas auricular fibrillation and other forms of arrhythmia are more common in the male. Cardiovascular disease is present in the male and female patients to the same degree.

The pulse rate tends to be slower in the male than in the female, while the pulse pressure is higher. It may be inferred, therefore, that the increased volume flow of blood is about the same in the two groups, although brought about by different mechanisms.

Various factors influence the frequency of palpitation and dyspnea and their severity.

Twenty-one patients with organic cardiac disease are analyzed. It is indicated that hyperthyroidism *per se* does not produce so-called thyroid heart disease but causes functional derangement in a cardiovascular system already damaged by other pathological conditions.

A superficial pleuro-pericardial friction rub heard over the sternum is described.

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(For discussion, see page 144.)

THE HEART IN HYPERTHYROIDISM: A CLINICAL AND EXPERIMENTAL STUDY*†

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THE cardiac manifestations of hyperthyroidism constitute a most prominent phase in this syndrome. Yet it is often difficult, sometimes impossible, to correlate the severity of these with the other clinical signs. At one extreme, signs of cardiac failure may be so conspicuous as to mask the concomitant hyperthyroidism. At the other, a patient may perish in the flame of a "thyroid crisis" without symptoms of myocardial insufficiency.

Tachycardia is frequently an early, and often a prominent, manifestation of the disease. Even more characteristic is the lability of the heart rate, such that it reflects exertion, excitement, emotion and fatigue to an unusual degree. Sooner or later, in nearly every case, this engenders "palpitation," which may vary in severity from an unusual awareness of the heart beat on the part of the patient during and following exertion to a most distressing, thumping, pounding sensation, which annoys the patient even at rest and renders exertion unbearable.

The blood pressure, like the heart rate, in such patients undergoes sudden and conspicuous variations. The studies of Fullerton and Harrop[3] indicate that, under basal conditions, neither the maximum pressure nor the pulse pressure is abnormal. During emotion or excitement the pulse pressure may greatly increase so that a systolic-diastolic difference of 80-100 mm. Hg is no uncommon finding. In the absence of coexistent vascular disease the diastolic pressure is rarely raised, indeed it may often be lowered; the systolic pressure is frequently elevated.

Both of these mechanisms (tachycardia and high pulse pressure) contribute to the increased circulatory minute-volume characteristic of any condition which augments the rate of metabolism.

The precordial impulse is diffuse, rapid and forceful. The apex impulse is frequently slapping; the sharp shock of closure of the pulmonic valves is often palpable. The relative cardiac dullness is sometimes demonstrably enlarged; particularly common is an enlargement to the left in the third and fourth interspaces. The heart sounds are loud and sharp; the first sound at the apex and the pulmonic second sound are often accentuated. Blowing systolic murmurs are frequently

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When read before the Annual Meeting of the American Heart Association, New Orleans, May 10, 1932, this paper was presented in two parts, "The Cardiac Manifestations of Hyperthyroidism" and "Experimental Observations Upon Hearts of Thyroxinized Animals."

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audible in the mitral and pulmonic areas. Fluoroscopy often reveals the enlargement of the cardiac shadow, particularly of the second curve to the left; especially striking is the visibly great amplitude of contraction of the ventricles.

It is a significant fact that none of these symptoms or signs are peculiar to hyperthyroidism. The diagnosis of what has been termed "thyroid-heart" is finally made, in the majority of instances, by demonstrating anatomical or functional abnormalities in the thyroid gland rather than in the heart. Particular importance attaches to the cardiovascular symptoms and signs for the reason that, in a certain proportion of cases, myocardial insufficiency supervenes. That, however, signs of congestive heart failure are often absent in what appear to be the most severe instances of the disease constitutes a perplexing phase of this clinical problem.

The present report deals with 200 cases of hyperthyroidism followed in the Johns Hopkins Hospital. All were carefully studied upon the medical wards, and after a suitable period of medical treatment, were subjected to subtotal thyroidectomy. The majority of cases returned to the medical wards for a period of postoperative observation.

According to the pathologist's report upon the portion of the thyroid gland removed, the cases were divided into two groups: exophthalmic goiter and adenomatous goiter with hyperthyroidism.

TABLE I.

	EXOPHTHALMIC GOITER	ADENOMATOUS GOITER
Total cases	158	42
Cases with cardiac failure	23	14
Average age	34.7 yr.	45.3 yr.
Average B.M.R.	+50.6	+42.6
Average duration of symptoms	12.6 mo.	22.4 mo.

Table I contrasts certain data concerning the two types. It is not our purpose to enter here into a discussion of the difference between exophthalmic goiter and "toxic adenoma." Suffice it to point out the greater age and duration of symptoms in the cases of nodular goiter. That these factors appear to combine to affect the reaction of the heart to this disease is indicated by the incidence of myocardial insufficiency in the two groups. Among 158 cases of exophthalmic goiter 23 or 14.55 per cent showed signs of congestive heart failure upon entering the hospital. The 42 cases of adenomatous goiter, on the other hand, included 14 (33⅓ per cent) with myocardial insufficiency.

In Chart 1 the incidence of congestive heart failure is related to the duration of symptoms.

Among all the cases of exophthalmic goiter in this series the average duration of symptoms of hyperthyroidism was 12.6 months. In those without cardiac failure it was eleven months, and in those with failure

the average duration of symptoms was 21+ months. In the group of what we have classified as adenomatous goiter there was usually a history of symptoms of hyperthyroidism for many months, often of goiter for years, and not infrequently a story of one or more previous attacks.

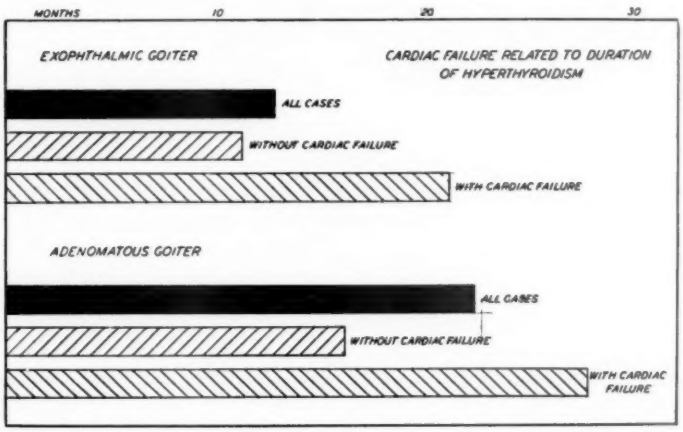

Chart 1.—Cardiac failure related to duration of symptoms among 200 cases of hyperthyroidism.

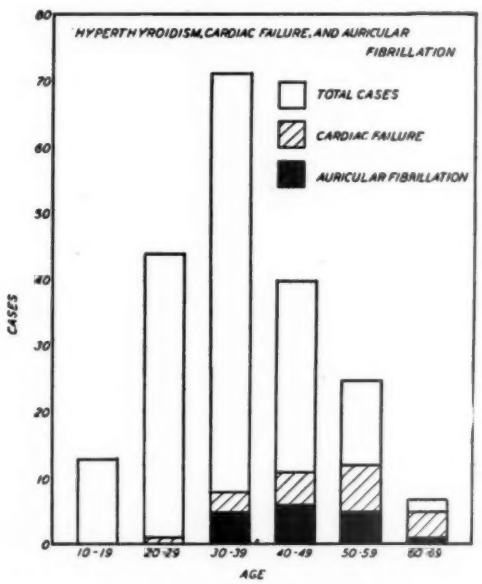

Chart 2.—Incidence of cardiac failure and auricular fibrillation among 200 cases of hyperthyroidism.

Here the average duration of symptoms was greater than in the first group: all cases, 22.4 months; with failure, twenty-eight months; without failure, sixteen months.

In Chart 2 is shown the occurrence of cardiac failure in this series. Each age decade above 30 includes a larger proportion of cases with

myocardial insufficiency; the incidence becomes conspicuously greater among those over forty years of age. This is to be ascribed to the natural diminution of the cardiac reserve which takes place with the years beyond forty and to the coincidence of organic—hypertensive, arteriosclerotic or rheumatic—cardiac disease with hyperthyroidism among the older patients in this series.

Among 112 cases of exophthalmic goiter and 16 cases of adenomatous goiter with hyperthyroidism under forty years of age, only nine showed signs of myocardial insufficiency. In five of these physical signs of mitral stenosis and insufficiency were demonstrable after the metabolic rate had fallen to normal. A sixth patient died; in this instance Aschoff bodies were demonstrated in the myocardium. Another patient, a young negress of twenty-six, who developed myocardial insufficiency with hyperthyroidism of only nine months' duration, had a positive Wassermann and signs of syphilis of the aorta. Thus, in 7 of these 9 cases there was found what was taken to be evidence of coexistent heart disease. All have been examined from twelve to eighteen months after discharge. The signs of organic cardiac disease persist.

Chart 2 also indicates that, in this series, established auricular fibrillation was associated with myocardial insufficiency in 17 cases. Transient periods of auricular fibrillation not uncommonly occurred in these patients. Such paroxysmal irregularities of the cardiac rhythm are not always associated with cardiac failure and frequently fail to recur following surgical relief of hyperthyroidism. Established auricular fibrillation is a much graver complication. The consequently irregular ventricular rhythm, unless its rate can be controlled with digitalis, presents a serious handicap to an already overburdened circulation.

EXPERIMENTAL

A series of observations have been conducted in this laboratory to study the effects of thyroxine* upon the hearts of animals:

1. *Effect of Thyroxine and Desiodothyroxine in Vitro.*—In some experiments, previously reported by Lewis and McEachern,[5] the auricles of normal rabbits were suspended in thoroughly oxygenated Ringer-Locke's solution in a Dale bath; in others the entire hearts of such animals were perfused with Ringer-Locke's solution by the Langendorff method. Thyroxine (Roche) added to the bath or to the perfusing solution produced no effect in concentrations up to 1/25,000. Desiodothyroxine (Harrington) was also without effect in concentrations up to 1/20,000. Such experiments were continued for as long as 8 hours during which the rate of the spontaneous rhythm gradually slowed; at no time was there any evidence of an augmenting action of thyroxine.

Recently Markowitz and Yater[6] have reported that cardiac muscle, explanted from the embryo chick after the first 48 hours of incubation, and

*The author desires to acknowledge the cooperation of Hoffmann-LaRoche, Inc. in furnishing a portion of the thyroxine used in these experiments.

incubated in the presence of 1/50,000 thyroxine, developed and sustained a more rapid spontaneous rhythm than control fragments of the same hearts which had not been exposed to thyroxine. It is of interest to note that even such a large dose of thyroxine produced its effect only after 12 hours' contact with the cardiac tissue.

2. *Physiological Properties of the Hearts of Thyroxinized Animals.*—Attempts to reproduce Graves' disease in animals by the administration of thyroxine have not, to our knowledge, met with success. It is, however, possible by such means to reproduce that phase of the syndrome which is due to hyperthyroidism.

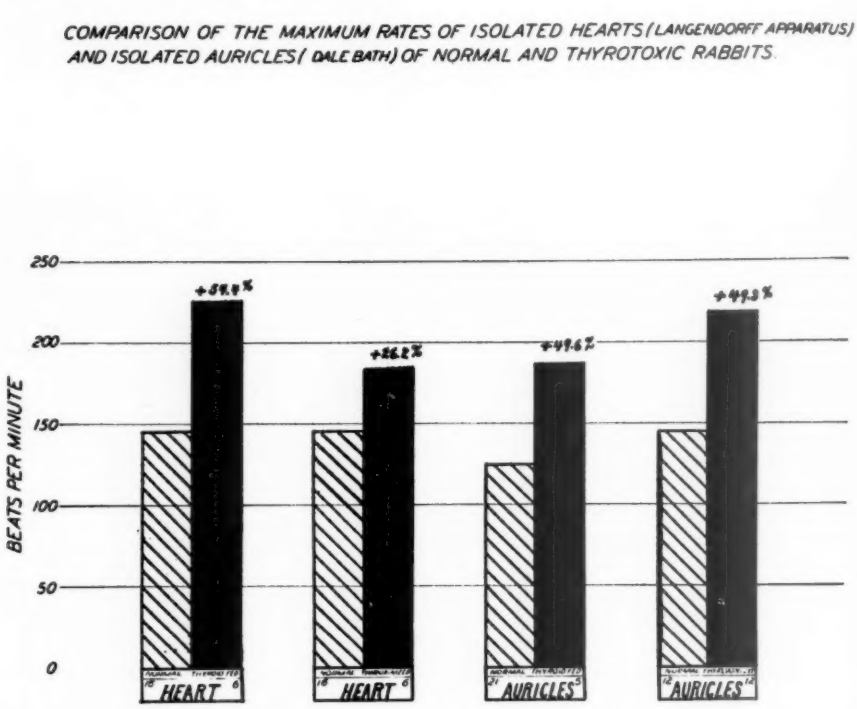

Chart 3.—Comparison of the maximum rates of isolated hearts (Langendorff apparatus) and isolated auricles (Dale bath) of normal and thyrotoxic rabbits.

If one injects into a rabbit 0.5 mg. thyroxine per kilogram body weight, events ensue which are homologous with the clinical signs of hyperthyroidism. During the first twenty-four hours after the injection no change may be noted. This "latent period" finds a clinical counterpart in the interval elapsing between the surgical removal of a portion of the thyroid gland from a patient with Graves' disease and the "postoperative storm" which not infrequently follows. By the end of 36 hours, however, the animal becomes more than usually responsive to stimuli, i. e., "nervous." Careful observation may reveal that his appetite and thirst increase. Furthermore, it may be demonstrated that, even when

he is at rest and undisturbed, his heart rate is abnormally rapid. Finally, it may be shown that his oxygen consumption (basal metabolism) has been augmented. If the dose of thyroxine is not repeated, these manifestations gradually disappear within the succeeding few days. If, however, such an animal receives a similar injection every other day, he rapidly loses weight, despite adequate amounts of food, and the tachycardia persists or increases.

It is a fact of considerable physiological importance that the effects of thyroxine persist in the hearts of such animals after isolation. Observations[5, 8] have already been reported from this laboratory showing that the hearts and auricles of thyroxinized rabbits continue to beat, when completely isolated, at rates much faster than those of similar preparations from normal animals. The results of a large series of such experiments are graphically shown in Chart 3. This tachycardia characteristically persists for hours, tending to decrease with time far less

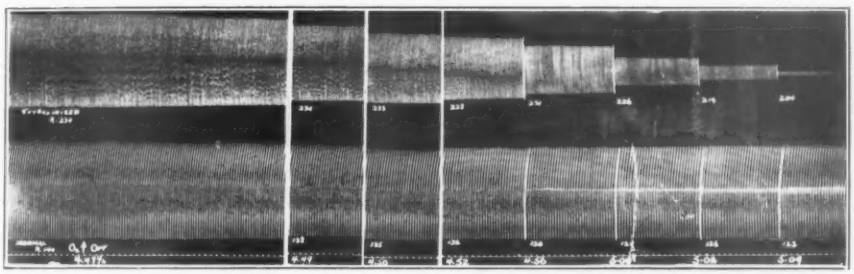

Fig. 1.—Effect of oxygen-want upon the auricles of normal and thyroxinized rabbits.

than the spontaneous rhythm of the isolated normal heart. This is in contrast with the tachycardia produced in animals by large doses of atropine or adrenalin, which subsides within a short time after isolation of the heart.

Further observations[8] indicate that the isolated auricles of thyroxinized rabbits are more dependent upon the contemporary oxygen supply than are similar preparations from normal animals. The kymographic tracing recorded in a typical experiment is shown in Fig. 1. The upper record is that written by means of a light lever by the auricles of a thyroxinized rabbit; the lower that of "normal" auricles. Both were suspended in oxygenated Ringer-Locke's solution in a Dale bath. In this experiment the auricles from the thyroxinized animal were beating at a rate of 234 per min., those of the normal at 140 per min. Interruption of the oxygen supply to the bath produced a conspicuously more pronounced effect upon the auricles from the animal which had received thyroxine.

By direct volumetric measurements it has been demonstrated[7] that the isolated auricles from thyroxinized guinea pigs consume more oxygen per

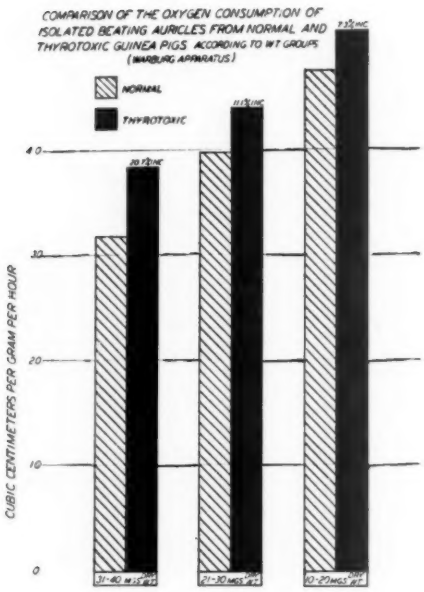

Chart 4.

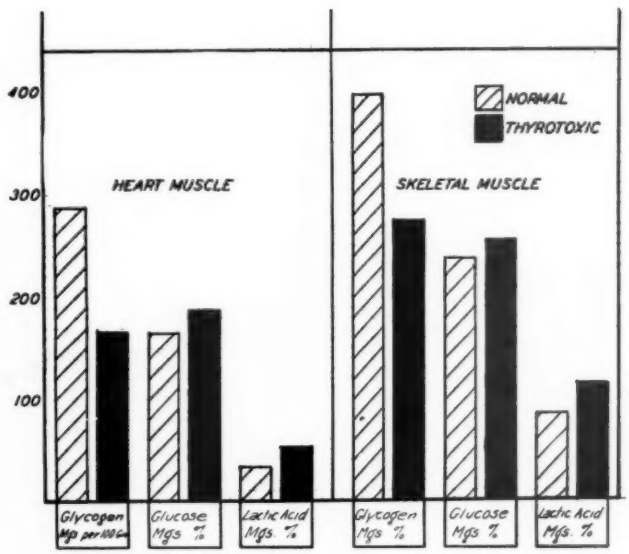

Chart 5.—Glycogen, glucose, and lactic acid content of cardiac and skeletal muscle from normal and thyroxinized animals.

gram per hour than those of the same weight removed from normal animals. These results of 31 experiments are summarized in Chart 4.

Dock and Lewis[2] have reported that the oxygen consumption per minute of heart-lung preparations from thyroid-fed rats is increased to the same extent as that of the entire animal. These authors state that such increase in the oxygen consumption of the heart-lung preparation can be accounted for by the increased weight and rate of beat of the heart of the thyroid-fed rat.

The discrepancy between the results summarized above and those of Dock and Lewis may be due, in part, to the difference in method. The guinea pig auricles in McEachern's experiments were surrounded and filled by fluid. Under these conditions the work performed is not significantly altered by change in rate of beat. In a number of instances the auricles ceased to beat during the period of observation. Under these circumstances no significant reduction in the rate of oxygen consumption occurred. This is in agreement with the observations of Clark and White,[1] who noted that the oxygen consumption of the auricles of cold-blooded animals was not significantly affected by rate of beat, provided no work was performed. In the heart-lung preparation, peripheral resistance and diastolic inflow remaining the same, a more rapid rate of beat is associated with an increase in the work performed.

That the metabolism of the myocardium is affected by the administration of thyroxine is further indicated by chemical estimations of certain constituents of the cardiac muscle of normal and thyroxinized rabbits. Chart 5 contrasts these results. The glycogen content of cardiac muscle is uniformly and conspicuously depleted by the action of thyroxine; the lactic acid content is increased in some instances. Similar alterations are demonstrable in the skeletal muscles of the same animals. That the glycogen content of skeletal muscle is depleted in thyroxinized animals has been previously noted.[4]

Such results do not in any fashion indicate that the heart is specifically or uniquely poisoned by thyroxine. They suggest rather that the metabolism of the myocardium is augmented thereby as is that of the skeletal muscle and other body tissues.

DISCUSSION

As has already been emphasized, the increased circulatory demands created by any conditions which augment metabolism increase conspicuously the work of the heart. In hyperthyroidism the metabolism of the myocardial tissue is also augmented. Conceivably these two factors combine in all cases, varying only in duration and degree, to bring to the fore the cardiac manifestations of the disease. The ultimate effect of these factors may be determined by the soil upon which they are implanted. In individuals whose circulatory reserve has been diminished by age or by organic cardiac disease they may result in myocardial in-

sufficiency. Presumably this may develop when the load thrown upon the myocardium exceeds or approaches the limits set by its own metabolism.

SUMMARY AND CONCLUSIONS

In a series of 200 cases of hyperthyroidism congestive heart failure occurred in 18.5 per cent. The average duration of symptoms was conspicuously greater in the cases with myocardial insufficiency. Its incidence increased in the age-decades above forty and was most common, in any age-group, in association with other, preexistent factors which tend to diminish the cardiac reserve: rheumatic heart disease, hypertension, arteriosclerosis or, more rarely, syphilitic heart disease.

Thyroxine 1/25,000 and desiodothyroxine 1/20,000 are without effect upon the isolated hearts or auricles of rabbits.

The administration of thyroxine to an animal (rabbit or guinea pig) so alters the metabolism of the myocardium that:

a. The heart beats at an enhanced rate for hours after isolation.

b. The oxygen consumption of the heart is increased, and

c. The glycogen content of the cardiac muscle is diminished; in certain instances the lactic acid content is increased.

It is suggested that myocardial insufficiency may supervene in hyperthyroidism when the load thrown upon the heart exceeds or approaches the limits set by its own metabolism.

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(For discussion, see page 144.)

THE HEART IN HYPERTHYROIDISM—AN EXPERIMENTAL STUDY*

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THE constant association of varying degrees of cardiac irregularity, observed in different grades of hyperthyroidism, has led to many clinical observations and studies of the morbid anatomy in an endeavor to ascertain the rôle of the secretory product (thyroxin) in the production of such disturbances. The characteristics of the increased pulse rate, the modification of the electrocardiogram and the increased volume output of the heart have been studied by Sturgis and Tompkins,[1] Barker and Richardson,[2] Smith and Colvin,[3] Hamilton,[4] Willius,[5] and Anderson.[6] These authors have concluded that the heart rate is proportionate to the degree of thyrotoxicosis. That as a result of the increased rate and volume outflow, in the presence of increased metabolism, the heart at first dilates and then later hypertrophies. If the hyperthyroidism persists gallop rhythm, extrasystoles, fibrillation and final dilatation. The question has arisen as to whether such cardiac irregularities are attributable solely to thyroxin or to other factors such as age, the superimposition of thyrotoxicosis in the presence of arteriosclerosis of the coronary arteries or previously existing myocarditis. Hurxthal[7] believes that there is a "specific heart drive" incited by thyrotoxicosis, while Lahey[8] holds the opposite opinion pointing to the absence of specific pathological changes in the hearts in such instances and the relative infrequency of cardiac irregularities in younger individuals as compared with those in middle or advanced age. A difference of opinion also exists as to the presence of specific changes in human hearts associated with hyperthyroidism. Fahr and Kuhle[9] and Goodpasture[10] hold that fatty and parenchymatous degeneration, perivascular round-cell infiltration, fibrosis and granulation tissue formation occurring in the hearts of instances of hyperthyroidism are specific. Baust[11] and others oppose this view stating that there is no constancy in the findings and that it is not possible to exclude other factors.

Experimentally induced hyperthyroidism has been equally unsuccessful in solving the problem of the heart lesions in hyperthyroidism. Goodpasture,[12] Cameron,[13] Hashimoto,[14] Takane[15] working with various animals (rabbits and white rats) were able to produce histocytes, round cells, perivascular necrosis and fibrosis in the heart muscle. On the other hand Lewis and McEachern[16] and Rake and McEachern[17] were not able to demonstrate specific lesions in the hearts of such experimental animals.

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*From the Departments of Pathology and Medicine of the University of Oregon Medical School.
Read by title.

It is therefore evident that neither the clinical nor the experimental data at hand are sufficient to settle the highly important question of the direct effect of the active principle of the thyroid gland upon the heart muscle in hyperthyroidism. Accordingly the following experiments were undertaken in an endeavor to further clarify this important and perplexing problem.

PROCEDURE

Twenty-four healthy Albino (white) rabbits were selected, weighed, housed in individual cages under careful sanitary conditions, and given standard prepared rabbit food (alfalfa especially prepared) once daily in sufficient amounts to maintain body weight under normal conditions. They were divided into four experimental groups as follows: Group I, Thyroxin fed and injected rabbits, Group II, Dessicated Thyroid (Armours) fed rabbits, Group III, Dessicated Thyroid (human thyroid glands from exophthalmic goiter) and Group IV controls. Six rabbits were placed in each group with the exception of the last in which there were five. In each of the Groups I, II, and III, two rabbits were thyroidectomized in order to remove the possible influence of the resident thyroid tissue. In addition one half of the animals (3 in each group) were given daily exercise by chasing them about in a large room for one hour. This was done to note the possible effect of additional strain upon the heart in the presence of hyperthyroidism.

The administration of the thyroid products was carried out by mixing them with the standard rabbit food and forming similar pellets which pellets were fed to the rabbits prior to the giving of the day's food portion. Great care was taken to see that each animal actually swallowed the daily dosage. The human thyroid tissue was obtained from 25 different thyrotoxic patients obtained through the courtesy of Dr. Thomas M. Joyce and Dr. Thomas D. Robertson of St. Vincent's Hospital and Dr. Charles Manlove of the Good Samaritan Hospital. These patients had an average metabolic rate of plus 27 and were given an average of 80 minims of Lugol's solution prior to the operation. The pathological diagnosis of all of these glands was diffuse parenchymatous hyperplasia (exophthalmic) with lugolization. The glands were cut into small pieces, dried and the fat removed with benzin. The residue was dried, pulverized and intimately mixed. Titration revealed the presence of 0.019 per cent of iodine in the final preparation.

All control animals were kept and fed exactly as were those given the various thyroid products. An attempt was made to produce a continuous accelerated heart action by cutting the depressor nerves and denuding the carotid arteries of the carotid sinus investment, without success except in one instance, most of the animals dying within 48 hours, usually of some intercurrent pulmonary infection. One rabbit so treated lived for 6 days. The cause of death was not grossly manifest. All operative procedures including the final taking of the pulse rates and blood pressures by inserting cannulas into the carotid arteries was done with the intravenous administration of sodium barbitol (2.0 c.c. of 11 per cent per kilo of body weight) and in addition light ether anesthesia for the skin incisions.

The dosage of all thyroid products was administered orally and was based upon the body weight of the rabbit in comparison with the dosage of dessicated thyroid gland ordinarily given to human beings. The amount was stepped up sufficiently to insure toxic manifestations. Accordingly the rabbits in Group I were given 0.6 mg. of thyroxin by mouth for a period of eleven days following which they were given 1.0 mg. intravenously for twelve more days. The dosage was increased and given by vein because marked toxic manifestations failed to develop by the oral method, also because the supply of available thyroxin was becoming limited. The rabbits in Group II (Armours Dessicated Thyroid) were given 0.4 gm. daily for eleven days,

0.6 gm. for three days and 0.8 gm. for nine days. The rabbits of Group III (Human "exophthalmic" dessicated thyroid) were given the same dosage for the same time as those in Group II.

COMMENT

Not all of the rabbits reacted uniformly to the administration of the thyroid products (see Chart I). In general there was a progressive increased irritability, loss of weight and increased pulse rate. The irritability was most marked in Group III (Human Dessicated Thyroid) and least in Group I (Thyroxin), probably because of inadequate dosage in the latter group. The loss of weight ranged from 60.0 gm. to 1320.0 gm. It averaged 512.0 gm. in Group I, 531.0 gm. in Group II, 856.6 gm. in Group III and 130.0 gm. in Group IV (Control group). The greatest loss occurred in Group III. A number of these rabbits

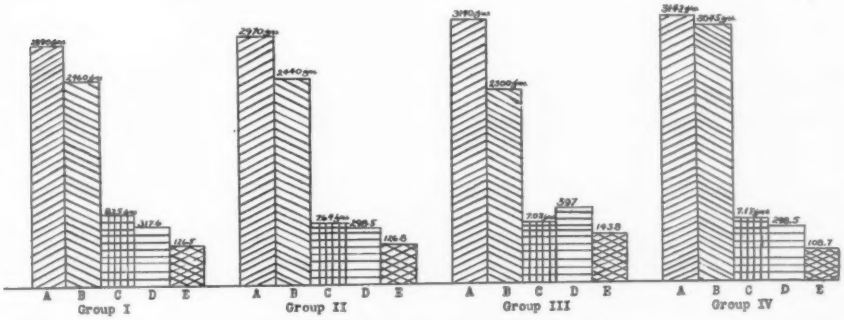
A B C D E
Group I
A B C D E
Group II
A B C D E
Group III
A B C D E
Group IV
Chart Illustrating the Comparative Relationships Existing Between
A- The average original weights
B- The average final body weights
C- The average weight of the hearts
D- The average final heart rates
E- The average final blood pressures

Chart I.—Illustrating the comparative relationships existing between *A*, the average original weights; *B*, the average final body weights; *C*, the average weight of the hearts; *D*, the average final heart rates, *E*, the average final blood pressures.

finally developed diarrhea with intense exhaustion. There was no doubt as to the evidence of a greatly increased metabolism accompanied by an increased respiratory rate and an accelerated heart action.

The pulse rate also increased progressively. It was taken daily throughout the experiment with the aid of the stethoscope. The rapidity of the heart action, which increased with the degree of thyrotoxicity, made it almost impossible to obtain an accurate count by this method. The beats appeared to be regular and full. There was no evidence of cyanosis of the mucous membranes of the mouth. The original pulse rate in Group I averaged 127.3, in Group II, 131.3, in Group III, 167.6 and in Group IV, 163. A consideration of the pulse rates taken with the stethoscope and finally with the recording drum indicates that the former method applied during the course of the experiment was inaccurate. While there was an increase of the heart rate in proportion to the degree of toxicity of the different experimental animals, there was no evidence of arrhythmia in the final recording. The pulse volume was

found to be smallest in those animals having the most marked increase in rate and the largest in those with slow rates. In the extremely thyrotoxic rabbits the heart exhibited signs of fatigue as indicated by the amplitude of the beats.

Considerable variation in the blood pressure was noted. It averaged 126.5 mm. Hg in Group I, 126.8 in Group II, 143.8 in Group III, and 106.2 in Group IV (The Control Group), the highest being 160 mm. Hg in a rabbit fed with dessicated human thyroid (exophthalmic), the lowest pressures being 115 in thyroid fed unoperated rabbits and 90 mm. Hg in thyroid fed thyroidectomized rabbits. In general the thyroid fed thyroidectomized rabbits had lower blood pressures; they averaged 117.6 mm. Hg as compared with an average of 142.3 mm. Hg in the thyroid fed non-thyroidectomized rabbits. This obvious increase in the blood pressures of thyrotoxic rabbits is in accord with the clinical findings in patients with hyperthyroidism, even when it occurs in younger patients in whom there is no reason to suspect other factors as a cause of the hypertension. One must therefore suspect that in hyperthyroidism clinically and experimentally the blood pressure is increased because of increased heart rate and possible angiospasm, probably due to either increased adrenalin output or excess metabolism (katabolism) or both.

All hearts with the exception of those from animals dying during the course of the experiments were weighed after being drained of their blood content. There was observed no constancy of relationship between the gross condition of the heart and the degree of toxicity of the animals. In general there was evidence of dilatation rather than hypertrophy. The chambers were large and the walls were proportionately thin. Although there were individual variations in the weights of the hearts in the different rabbits, the average weights in the 4 groups were found to be fairly constant (I—8.75 gm., II—7.64 gm., III—7.03 gm., IV—7.17 gm. respectively). The average heart weights of the first three groups when compared with the average original body weight established a ratio of 1 to 395.2 while the ratio between the average heart weights of the same groups and the average final body weights was found to be 1 to 314.8, a difference of 80.4 which in our estimation is largely due to the difference in body weights (original and final) rather than to a loss of weight in the hearts themselves. There was no gross evidence of disease in any of the hearts. In one or two instances the left ventricle appeared somewhat hypertrophic as compared with the right. Some of the hearts were long and narrow. The subepicardial fat was greatly diminished in the thyrotoxic rabbits as compared with those of the control animals. There was no detectable variation in the gross appearances of the hearts of the rabbits that were thyroidectomized or in those rabbits that were, in addition, exercised. There were no gross evidences of disease in any of the other organs or tissues of the rabbits as revealed by a general autopsy.

MICROSCOPIC STUDY

All sections of the tissues were stained with hematoxylin and eosin with additional van Giesen stains of the myocardium. The tissues and organs with the exception of the heart were studied mainly for the purpose of demonstrating the absence of other processes which might possibly explain the changes in the rabbits other than the induced hyperthyroidism. No disease processes were found. It was noted that the ovaries in the thyrotoxic rabbits apparently contained a greater number of so-called Call-Exner follicles than did the control animals.

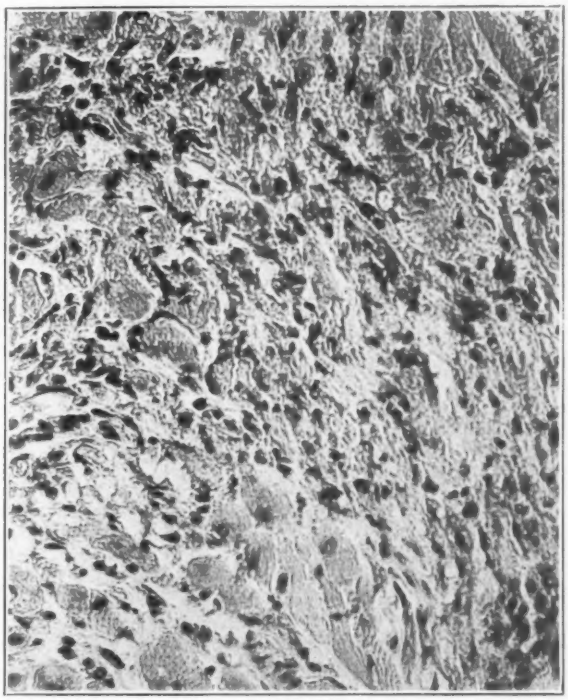

Fig. 1.—Photomicrograph No. 2. Rabbit No. 5. Illustrating the interstitial and perivascular diffusion of cells with the separation of muscle bundles.

For the study of the histology of the hearts sections were made through both ventricles at the apex, middle and base. In a number of instances of the hearts from the more pronouncedly thyrotoxic rabbits, every 300th section (10 mic.) was examined for the purpose of demonstrating the possible diffusion of disturbances. The histological changes in the hearts of the rabbits fed the different thyroid products varied considerably in the different animals. Such changes consisted of leucocyte invasion between the muscle bundles and about the blood vessels. These cells consisted of monocytes, plasma cells and eosinophiles. All but 4 of the 18 rabbits in Groups I, II and III exhibited such changes which were in some instances slight while in others such cell invasion was accom-

panied by some fibroblast proliferation with vacuole formation (fat) and fraying of the muscle bundles (see Figs, 1, 2, and 3). On the other hand only one of the rabbits in the control group exhibited such changes. This rabbit (No. 13) was one in which a tachycardia was produced by cutting the depressor nerves and destroying the carotid sinuses on both sides. This rabbit lived for six days. No gross pathological changes, except for a moderately enlarged heart, were found. Microscopically

Fig. 2.—Photomicrograph No. 2. Rabbit No. 9. Illustrating the cell invasion and fraying of muscle bundles.

marked cellular changes of the type described above (Thyrotoxic rabbit hearts) in the left ventricle were found. In none of the instances was fibrosis (scar tissue) *per se* found. There was no striking difference in the histological changes of the exercised rabbits as compared with those at rest. Neither was there any marked difference observed in the myocardium in those animals that were thyroidectomized prior to the induction of hyperthyroidism. The pathological changes were all confined to the left ventricle where they were diffusely scattered. They were not particularly pronounced in the papillary musculature.

DISCUSSION

There can be no doubt about the majority of the rabbits in the three groups having developed a state of hyperthyroidism within the range of individual susceptibility. The most striking evidence of the hyperthyroid state in the rabbits was the loss of weight, the increase of the pulse rate and the rise in the blood pressure. It seems fair to conclude that the whipping up of the metabolism leads directly or indirectly to an accelerated heart action which may eventually lead to cardiac exhaustion. The absence of pronounced cardiac hypertrophy in the rabbits and the more frequent occurrence of dilatation is in accord with the responses in the heart in human beings. It is estimated that it requires

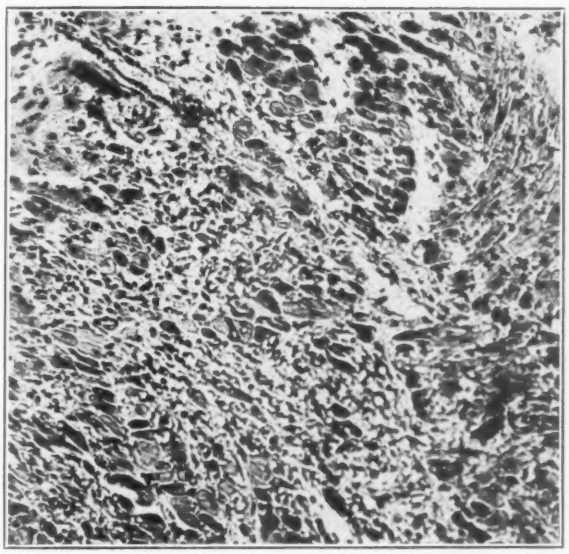

Fig. 3.—Photomicrograph No. 3. Rabbit No. 20. Illustrating extensive changes in myocardium.

approximately six weeks for hypertrophy of the heart to occur while these experiments extended over a period of twenty-three days. The striking absence of comparable pathological changes in the hearts of the control animals leads us to seriously consider cardiac damage in association with the induced hyperthyroid state in rabbits. As to whether this change in the heart is due to the actual impingment of thyroxin upon the cardiac circulation or musculature is difficult to determine. In arriving at a conclusion one must keep in mind the sequence of phenomena that evolve in the course of a slow or rapid perfusion of an excess thyroid secretion in the animal body. It seems to be a well established fact that metabolism (katabolism) is progressively and proportionately stimulated as a result of which the major body processes are augmented. Nutritional imbalance naturally follows. The glycogen reserve in the liver

(Willis and Mora[17]) as well as in the heart (De Fauw[18]) finally became exhausted. As this proceeds there occurs, according to Hsios-Chien Chang and others,[19] increased oxygen consumption and the increased transportation of metabolites, lead to the necessity of adjustment on the part of the circulation. There follows an increased pulse rate, augmented cardiac outflow, enlargement of the vascular bed and an increased blood volume. It is reasonable to conceive of the possibilities of the extra load placed upon the heart as eventually leading to fatigue and failure. It was in an endeavor to establish such factors that we provided the conditions of rest and exercise for our experimental animals, without success, probably because the conditions were not sufficiently sharply drawn. It occurred to us that the changes described might be related to the trauma of excessive, irregular and persistent overwork, on the part of the heart in the presence of hyperthyroidism, so that the myocardium might eventually undergo certain retrogressive changes (parenchymatous and fatty) on a nutritional basis. Further that such a degradation might lead to the tearing of muscle bundles and the secondary deposition of cells. Accordingly we attempted to provide a continuous acceleration and arrhythmia by cutting the depressor nerves and destroying the sinus caroticus bilaterally. Only one of our rabbits survived the operation sufficiently long (six days) to permit of cardiac damage. In this the changes were extremely marked and of the same type seen in the rabbits rendered thyrotoxic by feeding. We intend to investigate further this phase of the problem.

It must be remembered in evaluating the results of such experiments as are here delineated, that experimental conditions may not be entirely comparable with the incipient disposition of clinically acquired hyperthyroidism which implies a dosage of thyroid secretion and a time element that cannot be duplicated experimentally. Clinical evidence cannot be expected to solve the problem. Certainly the majority of instances described and commented upon in the literature fall in the age group (forty and above) in which many different disease ravages may be expected to mask or modify any specific change attributable to thyroxin. For the same reason the study of the pathology of human hearts in such instances of hyperthyroidism cannot lead to definite conclusions. One cannot ignore the fact that clinically there is some relationship between certain irregularities of the heart and hyperthyroidism and that such irregularities are amenable to correction in younger individuals while in older ones they may be permanent and incurable by therapy and thyroidectomy. Experimentally there seems to be no question that damage may be produced in the hearts of experimental animals. As to whether such changes as we found in our experiments are due to the actual toxicity of thyroxin, *per se*, or to greatly altered circulation and metabolism phenomena will have to be determined by more extensive controlled investigations.

SUMMARY

Experimentally produced hyperthyroidism in rabbits using (1) thyroxin, (2) Armour's dessicated thyroid and (3) dessicated human thyroid (from patients having exophthalmic goiter) for a period of 23 days resulted in the following changes in the hearts: parenchymatous and fatty degeneration, histiocyte invasion, fraying of the muscle bundles and early fibrosis.

It is possible that similar changes might be produced by cardiac overwork irrespective of the presence of an excess of thyroxin in the circulating blood as is indicated by the results obtained by cutting of the depressor nerves and denuding the carotid sinuses of their investments in order to allow the heart to operate uncontrolled.

There is no evidence in the literature to disprove the fact that a heart, that is induced to work more rapidly, with an increased volume output in the presence of increased pressure and metabolism (as is true in hyperthyroidism) may not exhaust its nutrition and respond with morbid anatomical changes that may be erroneously ascribed to the pernicious impingement of thyroxin on the myocardium.

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CARDIAC STATUS AFTER PROLONGED THYROTOXICOSIS*

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THERE seems to be a growing tendency to question the existence of the "thyroid heart" (of Kraus). Recent pathological studies of McEachern and Rake,[1] Thomas,[2] Cabot,[3] Lewis[4] and others have cast great doubt upon the significance of findings reported by Goodpasture,[5] Fahr and Kuhle,[6] Goodall and Rogers[7] and other workers which suggest that the hearts of patients dead of thyrotoxicosis show definite evidence of myocardial change. All of these pathological studies seem to be in agreement, however, that there is no change peculiar to thyrotoxicosis such as the characteristic lesions by which we identify rheumatic, luetic or arteriosclerotic heart disease.

Despite this lack of confirmation from the necropsy room, nevertheless, the impression seems to be generally prevalent that every thyrotoxic patient suffers a greater or lesser amount of myocardial damage. Thus the term "Hyperthyroid heart" is found in every classification of heart disease, and suggests that an intimate causal relationship exists between hyperthyroidism and the cardiac disorders which sometimes manifest themselves in thyrotoxic patients. Such a widespread clinical impression cannot be cast aside lightly. Where there is smoke there must be fire. Even though we suspect that the fire is a smudge fire and the excessive smoke therefrom is no sure measure of its size or heat we must investigate farther to discover the small flame of truth behind the widespread impression. Although demonstrable, organic evidence of cardiac damage is lacking yet it is possible that the heart is functionally impaired.

With the intention of ascertaining the amount and kind of functional impairment, I recently undertook a restudy of patients who were known to have been thyrotoxic for a prolonged period. This study was conducted in connection with a follow-up investigation of the late results of roentgen-ray therapy.[8] To the cases of that series I have added several patients who had been thyroidectomized, all of whom were known definitely to have run a prolonged thyrotoxic course, and some of whom still have high metabolic rates after as long as ten years after operation.

An intensive study of this group seemed to promise information of a kind not usually found in studies of the thyroid heart. If injury to the cardiovascular apparatus is a frequent sequel of thyrotoxicosis we might expect this group to reveal it. Such a group, while it presents some disadvantages also possesses an advantage in that those patients given roentgen therapy may be considered to have run a longer course of thyrotoxicosis than if this course had been shortened by thyroidectomy. A

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TABLE I

NAME	AGE	YEARS PT. WAS THYROTOXIC	HIGHEST B.M.R. PER CENT PLUS	YEARS SINCE ONSET	B.M.R. AT LAST EXAM.	P.R.	B.P.	CARDIOTHORACIC INDEX	HEART AREA			MURMUR	ECTOPIC BEATS	FAILURE		DIGITALIS	ELECTROCARDIOGRAM		
									PREDICTED	OBSERVED	DIFFERENCE			DYSPNEA	EDEMA		P-T INTERVAL	LEFT AXIS DEV.	T-WAVE INVERTED
Mrs. E. B.	44	½	23	11	−4	80	142/92	0.5	99	109	+10	0	0	+	0	0	0	+	III
Mrs. M. D.	54	5	112	10	−2	73	140/78	0.5	103	127	+24	0	0	0	0	0	0	0	III
Mrs. H. C.	50	½	67	10	−3	74	178/102	0.63	98	128	+30	0	0	+	0	0	Abn.	0	III
Mrs. E. C.	69	1	60	10	+2	68	160/100	0.5	98	119	+21	0	0	0	0	0	0	+	0
Mrs. R. B.	39	½	42	9	−1	71	124/86	0.44	89	92	+ 3	0	0	0	0	0	0	0	0
Mrs. B. M.	35	3	43	9	−1	72	134/90	0.45	109	98	−11	+	0	0	0	0	0	0	0
Mrs. B. S.	48	½	45	9	+4	78	120/76	0.6	102	107	+ 5	0	0	0	0	0	Abn.	+	0
Mrs. J. G.	55	4	46	11	+7	77	180/80	0.55	94	111	+17	0	+	0	0	0	Abn.	0	III
Mr. K. S.	43	3	66	7	−6	60	116/80	0.49	106	132	+26	0	0	0	0	0	0	+	III
Mrs. H. S.	45	2	?	23	−8	78	172/94	0.41	89	93	+ 4	0	0	0	0	0	0	0	0
Mrs. A. F.	43	3	54	3	+10	80	142/94	0.46	95	80	−15	0	0	0	0	0	0	0	0
Mrs. G. B.	55	6	55	6	+27	104	150/76	0.44	98	100	+ 2	+	0	+	+	+	+	0	0
Mrs. F. S.	30	4	23	4	+24	98	118/78	0.47	89	112	+23	0	0	0	0	0	0	0	0
Mrs. M. G.	28	2	69	Oper. 12/31	?	90	136/70	0.43	82	84	+ 2	+	0	0	0	0	0	0	0
Miss E. A.	58	11	33	11	+30	112	134/64	0.55	85	81	− 4	0	+	0	0	0	0	0	0
Miss M. M.	45	3	69	11	+20	76	146/96	0.51	101	102	+ 1	0	+	+	0	0	0	+	III
Mr. C. D.	48	6	61	7	−11	88	144/92	0.48	117	140	+23	0	0	0	0	0	0	0	0
Miss D. V.	15	1½	40	Died Post-op.		86	120/50	0.5	94	106	+12	+	0	0	0	0	0	0	III
Mrs. E. M.	61	3	38	4	−16	90	175/95	0.45	113	93	−20	0	0	0	0	0	0	+	0
Mr. W. C.	51	1½	33	2	−7	72	148/86	0.43	105	148	+43	0	0	0	0	0	0	0	0
MEAN	46	3	51	8¾		81	144/86	0.49			+9.8								

disadvantage exists, however, in estimating any cardiac damage caused by their former thyrotoxicosis because the time which has elapsed since they were thyrotoxic has seen many of them pass into the age of degenerative cardiovascular disease. This suggests that to estimate fairly the damage suffered by the heart in thyrotoxicosis we should confine our studies to patients under forty years of age. But when we recall that few, if any, thyroid-cardiacs are seen under forty we are led to suspect that the degenerative changes of the later decades are predisposing or complicating factors in the condition called "thyroid heart."

The data obtained from this follow-up study are shown in Table I where pertinent items obtained from an interval history and physical examination are supplemented by the objective findings of pulse rate, blood pressure, and heart size. An electrocardiogram was taken in every case and deviations from the normal are also recorded. Heart size was determined by a teleroentgenogram from which the cardio-thoracic index and cardiac area were measured.

The first ten patients may be considered as a group since all have normal metabolic rates from six to twenty-three years after treatment, and by every test may be regarded as entirely recovered from their thyroid disease. None of this group suffers from symptoms of cardiac disease. Two patients had dyspnea on exercise. One of these (E. B.) is twenty-five pounds overweight but her examination reveals no abnormal findings and she has a normal response to a simple functional test. The other patient (H. C.) has definite evidence of cardiovascular disease with blood pressure 178/102 mm. and enlarged heart, as well as electrocardiographic evidence of myocardial changes revealed in mild arborization block. This patient's age is fifty and she is known to come of a hypertensive family, which, with the very short course of thyrotoxicosis which she experienced, leads me to believe that her thyroid disease ten years ago played no part in producing her present hypertension. Her blood pressure at that time was normal.

Two others only in this group deserve comment. One (J. G.), fifty-five years of age, now has a systolic pressure of 180 and slight cardiac enlargement. One ectopic beat was noted at examination. This patient ran a long course, being under observation for over three years during which time she showed the characteristics, remissions and recrudescenses of Graves' disease. In September, 1921, she was observed to have a pulse irregularity which the electrocardiograph revealed as a progressive auriculo-ventricular block in which every seventh or eighth impulse was blocked. This block and inversion of the T-wave in all leads suggest that her physician was giving her digitalis. Her electrocardiogram at the present time is normal. With her systolic hypertension we might suspect that thyrotoxicosis was an etiological factor in her case. This patient, however, was known to have had a blood pressure of 165 to 190 before she came under observation for thyrotoxicosis.

The other patient (M. D.), presented, in 1922, the most critical case of Graves' disease I have ever seen. Her initial basal metabolic rate was a little above one hundred per cent. After two months of hospitalization and roentgen-ray therapy, resulting in marked improvement, the metabolic rate was still plus eighty per cent. This patient's case history has already been reported in detail elsewhere[19] and it suffices here to say that during the course of her thyrotoxicosis, which lasted over five years, she showed evidence of failing circulation in pitting edema of the feet and ankles. Now at the age of fifty-four this lady enjoys the best of health in every way, with no residuals of her former thyrotoxicosis and no signs or symptoms of circulatory disorder.

Included in this series are several patients who ran a very prolonged course, for reasons to be stated specifically for each case. Investigation of their circulatory systems for evidence of damage would seem to be a profitable procedure if the duration, rather than the intensity of thyrotoxicosis is the most potent factor in producing cardiac damage.[10] Most of these patients can be dismissed without comment as they show no evidence of cardiac damage.

One patient (G. B.) was seen in consultation in 1925 when she presented a classical picture of Graves' disease. She was having auricular fibrillation at the time and was considered too ill for surgical intervention. She improved under medical care but has never been considered a good surgical risk and is now quite comfortable though her basal metabolic rate is plus 27 per cent and she has paroxysms of auricular fibrillation. She has dyspnea and slight edema of the feet, which had been noted four years previously. The daytime pulse rate is a little over one hundred per minute and her systolic blood pressure is 150 with a normal diastolic pressure. The heart's size is not increased. The electrocardiogram also shows no abnormalities and resembles one taken four years ago except that the earlier tracing showed frequent ectopic beats.

One other case (E. A.) deserves mention because of her very prolonged thyrotoxicosis and her relative absence of cardiac signs and symptoms, although she is now fifty-eight years of age. She has suffered from thyrotoxicosis for over ten years, had two lobectomies in 1922 and has subsequently run a course marked by remissions and recrudescences with recorded basal rates as high as plus 33 per cent. She still presents signs and symptoms of toxic thyroid disease. She has no complaints referable to the heart and her blood pressure is 134/64 mm., with a suggestion of alternation noted when taking the systolic pressure. The heart size just exceeds the normal and the only electrocardiographic finding worth mentioning is slight widening of the QRS complex.

In summary it may be said that these patients who, from the duration and intensity of their thyroid disease might be expected to show the most characteristic and extreme cardiac damage, are singularly free from evidence thereof although they average forty-five years of age.

If one may draw the conclusion from this small group that there is scant evidence of serious, permanent cardiac damage in persons who have been thyrotoxic, there still remains the question: Whence comes all this cardiac smoke? Five years ago I[11] wrote that palpitation, tachycardia, arrythmias, hypertension, and congestive failure, usually with auricular fibrillation, are the clinical findings which suggest cardiac damage in these patients, and pointed out that the first three cannot be accepted as certain evidence of cardiovascular disease. Neither is there anything about the hypertension, which is found only in older patients, that distinguishes it from ordinary hypertensive cardiovascular disease found alone or coincidental with other pathological states.

Auricular fibrillation which occasionally supervenes in the course of a thyrotoxicosis is a definite sign of functional abnormality. Its advent in this disease, however, does not presage its likely continuance or have the same significance that it does in rheumatic mitral stenosis. It scarcely ever occurs in patients under thirty, is often paroxysmal in nature and usually disappears with subsidence of the underlying thyrotoxicosis.

Congestive failure, usually with auricular fibrillation, occurs in a small per cent of thyrotoxic patients and constitutes definite evidence of myocardial insufficiency. This does not necessarily imply structural myocardial change, however, for congestive failure may supervene in a heart rendered temporarily functionally insufficient, but which is organically sound. This fact finds, perhaps, its best illustration in those cases occasionally encountered in which the manifestations of congestive failure overshadow the underlying hyperthyroidism. The existence of these cases has been pointed out by Levine[12] in his reports upon "masked hyperthyroidism," where long existing thyrotoxicosis has exhausted the cardiac reserve and led to congestive failure. As further evidence that it is functionally exhausted and not organically damaged I quote Levine who says of these cases that there is "no other type of heart disease from which a patient may so satisfactorily recover after reaching the extreme state of cardiac failure." Only recently we had such a case (W. C.) on the Stanford Service at the San Francisco Hospital. He did not cease fibrillating after thyroidectomy, as was expected, so quinidine was started on the nineteenth day after operation. His fibrillation stopped after the initial dose of five grains and he has remained regular without further quinidine medication.

From the foregoing it seems logical to conclude that the "thyroid heart" is in reality a heart which has exhausted its reserve through maintaining an augmented blood flow over a period of months, and sometimes years.[11] It is one prematurely aged by overwork rather than one damaged by a specific thyroid toxin. This viewpoint finds support in the investigations of Willius and Boothby who say that auricular fibrillation depends on the duration rather than the intensity of thyro-

toxicosis. In an extensive and carefully controlled study of heart size in thyrotoxicosis, Hurxthal and his co-workers[13] found no definite relationship between cardiac enlargement and the duration of the thyroid disease. It is thus seen that there is no correlation between the severity of cardiac manifestations and the duration or intensity of hyperthyroidism. This brings me to the conclusion that inherent cardiovascular disease may be hastened in its development by the added work placed upon the heart in thyrotoxicosis; and that whether a toxic thyroid patient develops cardiac disease depends more upon the integrity of his cardiovascular system than upon the intensity or duration of his thyrotoxicosis. In addition I would emphasize that since the alleged thyroid-cardiac is nearly always past the age of forty years we should be cautious in assigning a previous, or coexisting thyroid disease as causative agent of the circulatory abnormalities which the patient presents.

SUMMARY

This is a clinical study aimed at ascertaining the amount of cardiac damage produced by hyperthyroidism. Since it is generally agreed that duration of the thyrotoxicosis, rather than its intensity, is the important factor in causing heart impairment, only cases of prolonged thyrotoxicosis are included here. The cases of twenty patients known to have been toxic for six months to eleven years were studied. Only one of these may be considered a cardiac cripple, and this patient had evidence of circulatory failure antedating the onset of thyrotoxicosis by four years. Two other patients (aged fifty and fifty-five years) had hypertension, which, from their histories could not be ascribed to their thyroid disease. There was no correlation between duration (or intensity) of thyrotoxicosis and heart size, blood pressure etc.

It was concluded that when cardiac failure supervened in the course of thyrotoxicosis it was a temporary functional insufficiency resulting from overwork (prolonged tachycardia, increased blood flow etc.), since there remained no evidence of permanent organic damage and because there is no characteristic pathological lesion. Further evidence in support of this view is that thyroid-cardiac disease is seldom, if ever, found in young people, but only in those in the later decades of life who have had their cardiac reserve already encroached upon by degenerative cardiovascular changes.

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MYXEDEMA HEART*

A Report Based Upon a Study of 17 Cases of Myxedema

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EIGHT years ago a woman aged forty-six years entered the Minneapolis General Hospital with the symptoms and signs of extremely severe heart failure; orthopnea, extreme anasarca, ascites, cyanosis, swollen liver (down 4 cm.), and passive congestion of the lungs. The heart was tremendously enlarged on teleroentgenographic examination, Ml. being 11.0 cm. and Mr. 8.0 cm. T. = 19.0 and total heart volume of 950 c.c. The electrocardiogram showed left preponderance, negative T_1 and iso-electric T_2. QRS duration = 0.18 sec. In addition the patient exhibited the symptoms and signs of a high grade myxedema: very slow speech, retarded cerebration, loss of memory, hoarse voice, dry and scaly skin, hair very sparse, dry and brittle, a sallow pallor of the skin with cyanotic patches over malar prominences, puffy eyelids with narrow lid slits, wrinkled forehead, all so typical of high grade myxedema. There was a very stubborn constipation. Basal rate even when associated with severe heart failure and dyspnea –25. Other data of interest; temperature 96-98, pulse rate 70. Blood pressure 110/70 mm. Red count 3,700,000, hemoglobin 75 per cent. Trace of albumin, few red cells and occasional hyaline and granular casts in urine.

The patient was given absolute rest in bed and put on fluid restriction and digitalis. No remission in the signs and symptoms of heart failure was observed on this treatment. Then large doses of thyroid extract (8 grams) were given and within a few days noticeable improvement in the symptoms of heart failure were noted. At the end of four weeks on thyroid extract, all dyspnea, lung edema and ascites had disappeared, the liver had receded to the costal margin; within twelve days the x-ray film showed the heart shadow 1.6 cm. smaller and in seven weeks' time the heart was normal in size, Ml. 8.6 Mr. 4.1 T. 12.7, heart volume 490 c.c. or one-half of its previous volume. The electrocardiogram became normal at the end of seven weeks. T_1 and T_2 were positive, the QRS time 0.08 secs. or 45 per cent as long as before thyroid treatment was instituted. The left preponderance had disappeared. The urine was free of albumin, casts and erythrocytes. The patient was now taken off thyroid medication and within seven weeks the heart had enlarged to Ml. 10.5 Mr. 5.5 T. 16, the T_1 and T_2 became negative, left preponderance appeared and the QRS became 0.16 sec. Moderate dyspnea and edema appeared and the liver came down below the costal margin. Thyroid was

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again administered and in six weeks the heart was normal in size, Ml. 8.5 Mr. 4.2 T. 12.7. The electrocardiogram showed T_1 and T_2 upright, the left preponderance no longer present, and the increased QRS time reduced to normal.

The patient remained practically free from heart failure symptoms for seven years. At times she would become careless about her treatment and then mild symptoms of myxedema would appear with lowered basal rate. At these periods heart failure symptoms would develop which would promptly disappear when thyroid extract in sufficient quantity was taken again. Two years after beginning treatment, the patient's blood pressure was 200/100 mm. and her basal metabolic rate 5 to 10 per cent above normal. On taking less thyroid the basal rate was brought down to −5 per cent but the blood pressure was up to 170/90. Moreover, the electrocardiogram showed a split and prolonged QRS of from 0.14-0.16 seconds. We feel that there is a very strong probability that this patient has a fairly high degree of coronary arteriosclerosis. In fact I believe it was present eight years ago when she first came under my observation. At that time I believe the coronary narrowing was very moderate. The split and prolonged QRS appeared then because of insufficient circulation in consequence of the drop in diastolic blood pressure as well as the drop in coronary flow associated with lowered minute volume. When the circulation improved on thyroid extract the diastolic blood pressure went up to 10-20 mm. Hg., the minute volume probably increased 50 per cent or more,[1] and the circulation through the coronaries was much improved so that the QRS time decreased in consequence of better blood flow to the heart muscle.* Later with increased narrowing of the coronaries a point was reached at which coronary flow was insufficient even with increased diastolic and systolic blood pressures. For the past four years the patient has been living in Oklahoma and writes me that she has some dyspnea and tires easily and notices a very moderate pitting edema of the extremities at bedtime. Although she has not been regular in taking her thyroid as she was previously, because of the difficulties of getting it immediately when her supply is exhausted, and probably is in need of better thyroid medication, yet I believe some of her cardiac symptoms are consequent upon coronary arteriosclerosis. I am hoping to have her come to Minneapolis for an examination in the near future.

No one can deny that the symptoms and signs of heart failure in this patient were largely consequent to the myxedema and were cured by thyroid medication after digitalis and rest in bed had failed. Her previous diagnosis made by very competent internists had been "myocarditis, chronic valvular disease, mitral insufficiency, myxedema." For

*Anrep[2] has shown that in the innervated heart-lung preparation if the diastolic pressure is kept constant, the coronary flow increases when the minute volume increases. The increase in coronary flow under these conditions is probably due to vasodilation reflexly produced.

me, the only real problem in this case is: how large a part did an associated coronary arteriosclerosis play? Certainly the amount of coronary disease present was in itself insufficient to produce heart failure. On the other hand it may very well have been an adjuvant factor and is now undoubtedly present along with a moderate degree of hypertension.

This case is a paradigm for five other cases of myxedema that I have seen in the past eight years, except that the electrocardiograms of the other cases showed normal QRS time. Eight cases of myxedema showed milder degrees of heart failure and less severe degrees of dilatation of the heart. But all of these eight cases showed some dyspnea, pitting edema, reduction of vital capacity, râles at the bases, dilatation of the heart on teleroentgenographic examination and very low iso-electric or negative T_1, all of which disappeared on thyroid medication; in six cases without any rest in bed. Three cases of myxedema showed no signs or symptoms of heart failure. One case had mild heart failure symptoms and a moderately dilated heart. He would not remain under treatment long enough to find out whether the signs and symptoms of heart failure would recede under thyroid medication. Therefore we can sum up by saying that out of 17 cases of severe and moderately severe myxedema, 13 or 75 per cent showed symptoms and signs of heart failure, all of which disappeared after giving thyroid extract. The symptoms and signs were extremely severe in five (30 per cent) of our cases. I believe that these figures gathered from a study of seventeen cases give a fair representation of the status of myxedema heart or heart failure in hypothyroidism; namely 70-75 per cent will show some symptoms and 30 per cent will show a very severe degree of heart failure. Our oldest case was 70 years of age at the time symptoms and signs of myxedema and heart failure developed. Our youngest case developed symptoms and signs of heart failure and myxedema at 19 years of age. The arithmetical mean age for our 17 cases is 45 years for the approximate onset of myxedema heart.

There is to my mind no question as to what constitutes the proper therapy in most of these cases—thyroid extract sufficient to bring the basal rate to –5 to 0. When coronary disease seems definitely established, I would add a theophyllin derivative to dilate the coronaries. There is no objection to the use of euphyllin or other coronary dilators even when the diagnosis of coronary narrowing is not definitely established. I feel that digitalis is of little value in most of these cases. I have taken patients off thyroid, allowed them to become decompensated and then have tried the effect of digitalis in adequate dosage upon the case for periods of from two to three weeks, without a measurable effect. Thyroid would always show a definite effect upon these cases within an equal period of time.

Up to the present time no adequate explanation of myxedema heart has been given. Some years ago Sutherland Simpson of Cornell pro-

duced cretin sheep and goats by removal of the thyroid shortly after birth. Seventeen of these sheep and three of the thyroidectomized goats were given an autopsy examination by S. A. Goldberg,[3] Professor of Pathology at Cornell Veterinary College. These animals had lived from approximately one to two years after the thyroidectomy. Causes of death were not stated, some were merely killed for autopsy purposes. At autopsy, the signs of ascites, anasarca, hydrothorax, hydropericardium, passive congestion of liver, passive congestion of lungs with lung edema, and passive congestion of the kidneys, one or more were found in 70 per cent of the animals. In a number of instances normal litter mates used as controls were autopsied at the same time. The controls never showed the above signs. All of the cretin animals showed arteriosclerosis and atherosclerosis of the large arteries with fusiform dilatation and lengthening, none of the controls did. The diagnosis of arteriosclerosis was made both macroscopically and microscopically. The majority of the animals showed anasarca, hydrothorax, and ascites. Only one showed a passive congested liver. But it is to be remembered that nothing is said about the livers in the other animals. The hearts of nearly all the animals are described as dilated, flabby, and pale. Goldberg also states that in the heart muscle of a number of these cretin animals, cross striation was absent, the muscle fibers were not normal in appearance. In this connection, it is to be remembered that Sutherland Simpson's daughter,[4] Ethel, studying the voluntary muscles of the sheep, found that there was a distinct difference, namely that the cytoplasm of the muscles was very definitely in smaller quantity in the cretin sheep. The nuclei of the muscles in the cretin sheep were in much smaller number than in the normals.

If these autopsy examinations are to be accepted, then myxedema which was present in these cretin animals is frequently accompanied by signs of heart failure, of arteriosclerosis, and of changes in the heart and heart muscle which might be interpreted as due to or accompanying heart failure.

Kurt Felix[5] has reported upon some experiments carried out under Friedrich Mueller in which it seemed to have been shown that thyroxin added to the perfusion fluid of an isolated frog's heart increased the amplitude of the beat or in other words, the work done per beat. Dynamometer and ergograph examinations of the voluntary muscles of myxedema patients from this clinic carried out by Professor Rockwell of the Department of Psychology of the University of Minnesota, show that the strength of the voluntary muscles is definitely reduced in myxedema and that myxedema muscles fatigue much more rapidly than the same muscles after thyroid treatment of the patient. It is not difficult to imagine that lack of thyroid hormone which leads to weakening and increased susceptibility to fatigue of skeletal muscle will lead to the same functional changes in heart muscle. There seems to be enough

experimental evidence then to make it seem very probable that lack of thyroid hormone weakens the heart and results in heart failure.

We are inclined to believe that not a few of these patients have some degree of coronary arteriosclerosis usually not of such a degree as to cause heart failure, but possibly aiding in the production of heart failure when myxedema develops and coronary flow falls because of the drop in diastolic pressure and because of the drop in minute volume. On the other hand the coronary arteriosclerosis is not to be assumed as the main

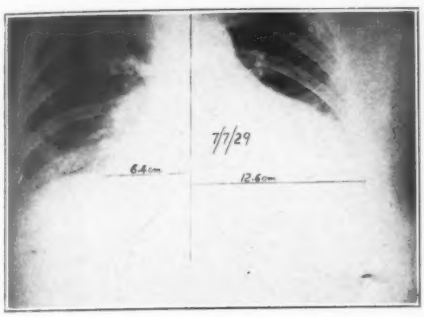

Fig. 1.

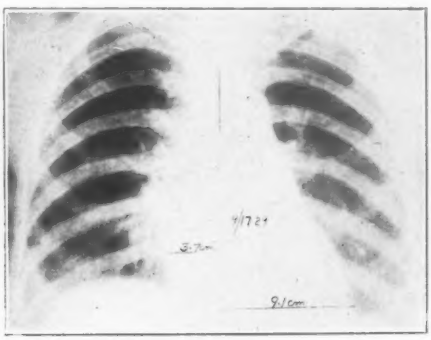

Fig. 2.

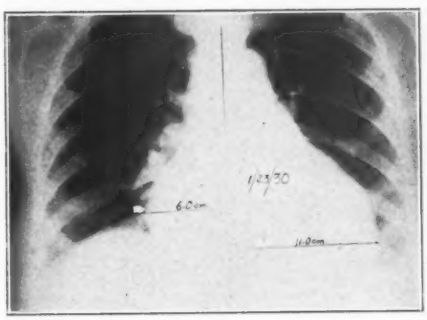

Fig. 3.

Fig. 1.*—Teleroentgenogram of a patient with myxedema on entrance; basal metabolism −27 per cent. Two weeks on large doses of digitalis had no effect upon heart failure signs and symptoms.

Fig. 2.—Teleroentgenogram of same patient taken nine weeks later after being on thyroid extract for seven weeks; basal rate +15 per cent. Heart failure signs and symptoms gone.

Fig. 3.—Same heart after four months' withdrawal of thyroid extract; basal rate −32 per cent. Decompensation symptoms present.

factor in the production of heart failure in myxedema. One of our patients developed myxedema and heart failure at the age of 19 and in this case there is no reason whatsoever to assume coronary arteriosclerosis.

It is of considerable interest to know how long it takes to develop the severest grade of dilatation of the heart and heart failure symptoms after the function of the thyroid ceases. Zondek[3] has reported upon a

*These illustrations are from a paper on Myxedema Heart by Jay Davis, Ann. Int. Med. 4: 733, 1931, and are reproduced with his permission.

case of a German officer who was shot through the thyroid gland in December 1914. Abscesses formed in the thyroid, destroying the gland. Approximately a year after the injury to the thyroid gland, symptoms of mild myxedema had developed and also a mild degree of dyspnea.

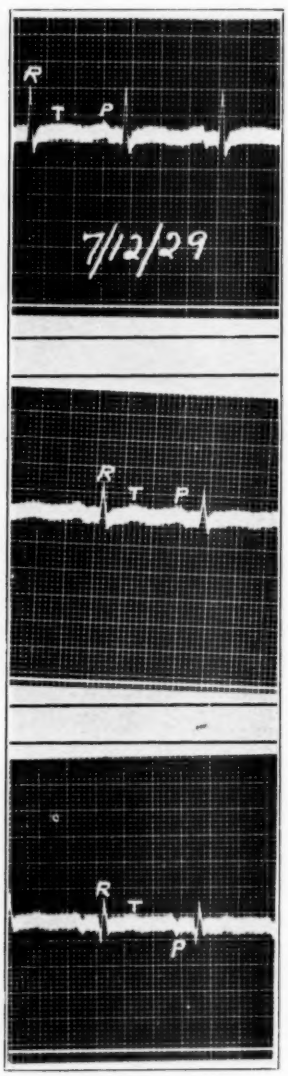

Fig. 4.

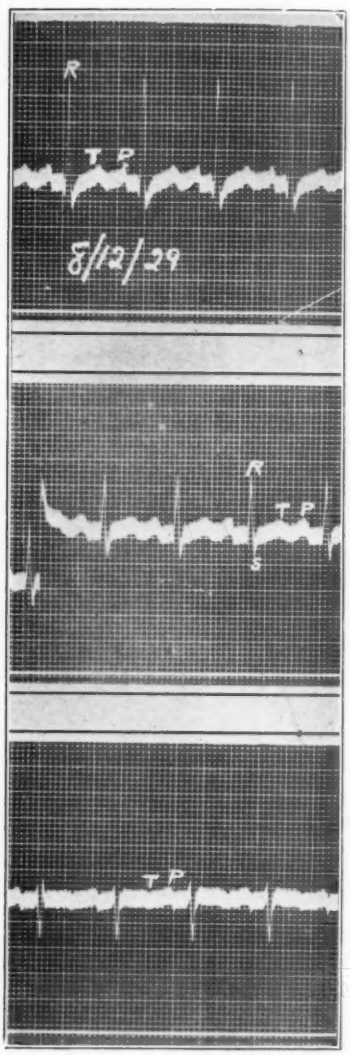

Fig. 5.

Fig. 4.—Electrocardiogram corresponding to Fig. 1.
Fig. 5.—Electrocardiogram after thyroid treatment.

But it was three years after destruction of the thyroid gland before the severe stage of heart failure had finally developed.

The patient whose teleroentgenograms and electrocardiograms illustrate this paper was on thyroid extract for one year, at which time

there were no symptoms or signs of myxedema or of heart failure and the heart was normal in size, the transverse diameter being 12.9 and the basal rate + 3. The patient was then taken off thyroid extract and the basal rate immediately dropped, and within ten weeks' time was down to

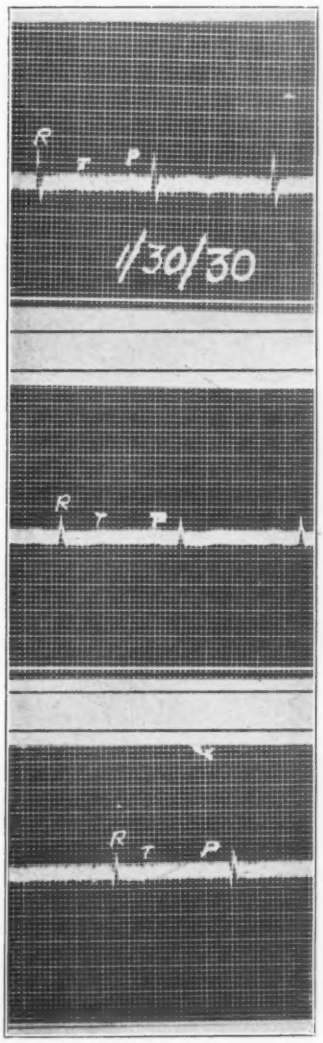

Fig. 6.—Electrocardiogram after withdrawal of thyroid extract.

–30. The patient was under constant observation in the wards of the hospital. No change of any kind was noted until about 12 weeks after thyroid treatment had been discontinued when the nurses reported that she was moving about more slowly and seemed to be less active. Very very slowly only did symptoms of myxedema develop. In fact, it was about

five months after discontinuing the thyroid treatment that the slowing up in cerebration and in physical activities became outspoken. Four months after discontinuing the thyroid extract, a little pitting edema along the shin bone could be made out and about this time the nurses and doctors noted that the skin was becoming dry. Two months after discontinuing thyroid extract, the heart was approximately the same in its size. Five months after discontinuing thyroid extract the heart had only dilated 1.6 cm. in transverse diameter. It was approximately eight months before the heart had dilated out about 3 cm. and dyspnea on exertion was fairly marked, the edema was moderately severe, and there were a few râles present in the bases of the lungs. Thyroid treatment was begun before the severest stage of heart failure was reached.

We feel certain that it would have taken a year or more before the heart would have attained its original transverse diameter and the symptoms of heart failure would have increased to their original severity. It is interesting to note that ten weeks after discontinuing the thyroid extract, the first signs of change in the electrocardiogram showed up. T_1 was then just barely positive. This experiment indicates that when the thyroid hormone is no longer supplied to a patient who has been supplied with sufficient thyroid hormone for a year or more, the mental symptoms of myxedema begin to develop within a few weeks. Skin changes appear a little bit later and are very slow in developing. But the changes in the heart, although they are indicated within a few months after discontinuing thyroid, yet it is many months before they develop to their extreme degree. Our patient living in the hospital had few calls upon her physical activities and it is barely possible that, if she had been at home and compelled to carry out more physical activity, the heart would have dilated more rapidly. Our studies seem to indicate that the severest grades of myxedema heart are only found in patients who have been in a hypothyroid state for a number of years. Where we are fairly certain that the hypothyroidism has developed within a period of less than a year or where the hypothyroidism is of mild degree, there we have noted that the dilatation of the heart and the symptoms of heart failure are of very moderate extent. Undoubtedly patients who for one reason or another are compelled to carry out considerable physical activity develop their symptoms more rapidly than those who can slow down their physical activities when the slowing down of mental activity takes place.

Christian[6] has insisted that thyroid treatment may be dangerous in the treatment of myxedema associated with heart failure. I wish to report on a case of myxedema with heart failure complicated by a severe degree of coronary arteriosclerosis with improvement in the symptoms of congestive heart failure on thyroid treatment but ending in death from coronary thrombosis four months after beginning the thyroid medication. This case will not only serve to point out the danger associated

with thyroid treatment but will, I think, show why thyroid treatment is occasionally dangerous in these cases.

This patient, a female, forty-six years old, came to the University dispensary complaining of slow speech, slow activities, both mental and physical, loss of memory, mental depression, hoarseness, dry thick skin, loss of hair, cold hands and feet, all of about two years' duration, having gradually developed to the present degree. For the past two months she had noticed shortness of breath with swelling of ankles. She had several attacks of severe precordial pain the past four months. During these attacks she was very much frightened and was afraid she would die. These attacks sometimes came on without exertion, but more frequently after exertion and were then relieved on resting.

On examination the patient talked very slowly, skin was dry, hair was very thin, skin over face was sallow with cyanotic spots on the cheeks, face and eyes swollen, narrow lid slits, finely wrinkled forehead, nose broadened, lips and tongue swollen, no typical myxedema of skin seen or felt, but rather dry, wrinkled and with distinct loss of turgor. There was slight pitting edema of the legs, liver down below the costal margin one fingerbreadth, râles at both lung bases. Orthodiagram showed a generally dilated flabby heart; Ml. = 10.3 Mr. = 8.3 T. = 18.6. Transverse thoracic diameter = 23.0 cm. The lungs showed the fluoroscopic signs of passive congestion. The electrocardiogram taken at this time has been lost but the notes of the physician who read the electrocardiogram state "Delayed intraventricular conduction, QRS = 0.12, left preponderance, low broad T_1." Basal metabolism at this time when some dyspnea was present −20. One taken six days later was −25. The blood pressure was 140/104. The patient was put on 1 grain of Armour and Company's thyroid extract twice a day. Six days later she entered the Minneapolis General Hospital. In the six days' interim the patient had taken only a small amount of the thyroid extract prescribed. She was extremely nervous and apprehensive and was extremely difficult to manage, in contradistinction to the average case of high grade myxedema. On the first hospital day she had anginal attacks which were only relieved by morphine. Throughout her stay in the hospital, the patient had frequent attacks of nausea and vomiting. Two grains of thyroid extract a day were administered. In addition 0.1 gram Euphyllin five times a day to dilate the coronaries. There were no more anginal attacks until on the eleventh day when she had another severe attack, unrelieved by amyl nitrite but relieved by morphine. From this time on until her death, attacks of angina were present nearly every day and sometimes there were two or three attacks in one twenty-four hour period. Some of these attacks lasted forty-five minutes and were only relieved by large doses of morphine. There were some days on which no attacks appeared but the patient was undoubtedly in a "status anginosus." The blood pressure which was 148/100 mm. on the day of admission dropped to 104/80 mm. on the fourth day in the hospital and from this time on the diastolic pressure varied between 60 and 80 mm. Hg. The vital capacity which was 1400 c.c. on admission went up to 2000 c.c. or 80 per cent of her calculated normal within three weeks. In the meantime her edema disappeared, the liver receded behind the rib margin and the heart went down to Ml. = 9.2 Mr. = 5.9 T. = 15.1 within five weeks' time a recession of 3.6 cm. in transverse diameter. It never got any smaller than this so that part of the dilatation in this heart was not influenced by thyroid medication and therefore was probably due to another cause. The basal metabolism was normal within about six weeks after entrance to the hospital. The electrocardiogram which showed a depressed S-T interval in the first lead ending in a T_1 which only rose 0.5 mm. above the iso-electric line showed very little change after thyroid medication. We concluded from this that coronary arteriosclerosis was probably present in this case in addition to myxedema.

For a time the patient seemed compensated and the anginal attacks became infrequent. It appeared as if the patient might be improving. But about three months after admission the anginal attacks became very frequent, orthopnea set in, the heart was shown to be dilated on x-ray examination. Three weeks later the patient died suddenly. Autopsy was limited to the heart. This weighed 475 grams. There was almost complete occlusion of the left descending branch of the coronary artery with a thrombus farther down in the lumen. The other two branches were narrowed. There was a necrosis of the heart muscle in the left ventricle indicating a thrombosis which must have been present for a few days. There was also a large mural thrombus in the left ventricle. There was fibrosis of the rest of the myocardium. It is possible that a piece of the mural thrombus became free and caused a cerebral embolus with sudden death.

It is no longer a question in my own mind that this patient should not have been given thyroid medication. The number of attacks of angina pectoris increased after giving thyroid treatment and very probably because of the thyroid. Autopsy showed that the patient had a severe degree of coronary arteriosclerosis. That part of the coronary system which dilates considerably when minute volume increases could not dilate in this heart. Therefore there was no increased flow of blood through these coronary vessels when the minute volume put out by this heart increased 50-100 per cent or more and the mechanical work of the heart muscle increased correspondingly. Moreover the drop in diastolic blood pressure which took place after the patient was put to bed in the hospital was a factor tending to reduce blood flow through these narrowed coronaries. We must not forget that there is flow through the coronaries during systole as well as diastole in feebly beating hearts whereas in vigorously contracting hearts, flow takes place almost entirely in diastole. The myxedema heart is a feebly beating heart and if the coronary arteries are hardened and no longer able to dilate and if the diastolic blood pressure does not rise, the flow through the coronaries is better in it than in the same heart after treating with thyroid extract and producing a stronger contraction. The blood supply to the heart muscle in relation to the work performed was very probably much less after than before giving thyroid extract. Probably in consequence of this, the attacks of angina pectoris increased in number. Probably the reduced volume of flow through the coronaries aided in the formation of the thrombus. We are compelled to admit that thyroid medication might better have been omitted in the treatment of this patient. On the other hand, I believe that thyroid extract should be given to patients with myxedema and coronary disease provided no angina pectoris is produced and provided the heart shows signs of better function. Not infrequently angina pectoris attacks disappear after thyroid treatment is started in myxedema. In these cases we must assume the coronaries can still dilate when minute volume increases. Moreover in most cases the diastolic pressure rises after giving thyroid extract and in consequence the coronary flow increases proportionately to this increase in diastolic pressure. It is a matter for the judgment of the clinician to decide

when to give and when not to give thyroid extract. It is nearly always safe to try thyroid extract out and base the medication upon the phenomena produced by it.

SUMMARY AND CONCLUSIONS

Seventy-five per cent of all of our cases of myxedema show some signs and symptoms of heart failure. Thirty per cent of all our cases of myxedema show very severe symptoms and signs of heart failure. The volume of the heart in these severe cases is increased approximately 100 per cent.

Thyroid extract relieves the symptoms and signs of heart failure promptly. Digitalis is of doubtful value. Many cases of myxedema heart are complicated by coronary arteriosclerosis. If the coronary narrowing is extensive, thyroid extract treatment may be contraindicated because the coronary flow may decrease at the same time that the mechanical work of the heart increases. In these cases if angina pectoris develops after treatment with thyroid extract or increases in frequency and in intensity or if the heart failure symptoms do not decrease, then thyroid extract should not be given or should be given in reduced amount.

The age of onset of myxedema heart varied between nineteen and seventy years of age. The average age being forty-five at onset.

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(For discussion, see page 146.)

CONGESTIVE HEART FAILURE AND HYPERTROPHY IN HYPERTHYROIDISM: A CLINICAL AND PATHOLOGICAL STUDY OF 178 FATAL CASES*

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IN ANY study of cardiac hypertrophy the selection of a standard by which hypertrophy may be measured is of the greatest significance, as it is obvious that the integrity of one's conclusions depends almost entirely on such a standard. Cardiac hypertrophy in hyperthyroidism would practically cease to be a problem if a universally accepted standard for the weight of the normal heart were available. Bell and Hartzell,[1] in 1924, discredited practically all the standards published up to that time by showing that the increase in the average size of the heart after the fourth decade was due largely to the inclusion of cases of hypertension. Smith,[3] in 1928, found that there was no relationship between age alone and weight of the heart, but that there was a definite correlation between the weight of the heart and the weight of the body if cases of hypertension and cardiac disease *per se* were excluded. At the same time he formulated a standard for cardiac weight based on bodily weight. In the present study we compared the weight of the heart at necropsy to Smith's maximal normal value for the usual weight of the patient prior to illness. It is probable that hearts weighing more than Smith's upper limit of normal values are hypertrophied.

It is almost self-evident that in the presence of hyperthyroidism the weight of the heart will depend on: (1) the weight of the heart before the onset of hyperthyroidism, and (2) any change in that weight which the hyperthyroidism might produce. Theoretically, at least, it is conceivable that hyperthyroidism might result in either an increase in cardiac weight as the result of increasing the work of each beat, or, under some circumstances, in a decrease as the result of malnutrition. There is little doubt that malnutrition in non-hyperthyroid states may result in cardiac atrophy. The hearts of patients dying of wasting diseases are usually small; victims of famine have been found to have small hearts, and in inanition, experimentally produced, cardiac atrophy can be demonstrated. A complete consideration of the effects of inanition on the heart may be found in the work of Jackson[2] on this subject. There is ample evidence in our material to indicate that loss of bodily weight in hyperthyroidism may be a factor in the determination of cardiac weight. Certainly the effect of malnutrition cannot be dismissed lightly when one considers that the average loss of bodily weight in our cases was about 25 per cent, and in some instances as high as 50 per cent.

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To present the problem more concretely the case is presented of a woman, aged sixty years, who came to The Mayo Clinic because of persistent exophthalmic goiter following thyroidectomy six years previously. Her usual weight was 135 pounds. At the time of death she weighed 67 pounds, a loss of 50 per cent. According to Smith's standard the weight of her heart before she was taken ill should have been between 203 and 286 gm. What was happening to the weight of her heart while her bodily weight was decreasing to 50 per cent of its former amount? If there were no other factors at work, her heart in all likelihood would lose a considerable portion of its weight. How much it would have lost we do not know. But during her illness her heart was confronted with the burden of mobilizing metabolites at a rate of 98 per cent more than normal. At death the heart weighed 300 gm., 14 gm. more than Smith's maximal value for a woman weighing 135 pounds. What conclusions are we justified in drawing from cases of this type? Can we conclude that the heart was spared while the body as a whole lost weight, or that the heart hypertrophied to the extent of 14 gm., or that the heart would have been much larger had not the loss of bodily weight tended to prevent hypertrophy? The present study was undertaken with the hope that we might be able to sharpen our conceptions of the problem, rather than to formulate any final opinions.

The material for study consisted of 110 fatal cases of exophthalmic goiter and sixty-eight fatal cases of hyperfunctioning adenomatous goiter, observed at The Mayo Clinic over a period of ten years ending January, 1931. In all instances the clinical diagnosis was verified by histological examination of the thyroid gland. Complete necropsy was performed in each case. In the entire group there were 129 females and forty-nine males, distributed through all the decades from the second to the eighth inclusive. Except for eleven patients aged more than sixty years, the cases of exophthalmic goiter can be divided into three groups approximately equal in number: patients aged less than forty years; patients aged between forty and fifty years, and patients aged between fifty and sixty years. Except for ten patients aged less than fifty years and two aged more than seventy, the patients with hyperfunctioning adenomatous goiter were distributed about equally in the sixth and seventh decades; twenty-five of the entire series were aged less than thirty-five years. The latter group was studied separately because of the relative infrequence of hypertension and degenerative lesions of the heart occurring in patients of this age. The relatively large number of fatal cases of exophthalmic goiter among young persons can be explained by the fact that although the series of cases extends over a period of ten years, compound solution of iodine in the treatment of exophthalmic goiter was in use as a routine only in the last eight years of the period.

Most of the patients had suffered from severe hyperthyroidism, as shown by the fact that only twenty-four of the patients with exoph-

thalmic goiter had determinations of basal metabolic rate lower than +50 per cent.

It is important to evaluate carefully the facts regarding the material which we have used for study, as, in a sense, it is selected. Since it is relatively unusual for hyperthyroidism to terminate fatally, a consideration of post-mortem observations alone may possibly lead to a distorted picture of the disease as it usually occurs. Furthermore, we are considering cases in which, as a group, severe long standing hyperthyroidism had been present, and our conclusions therefore may not apply to mild cases of short duration.

Of the 178 cases, eighty-eight (49 per cent) had to be excluded from the study of hypertrophy because of hypertension, recognized clinically or because of intrinsic disease of the heart recognized at post-mortem examination. One case was excluded because the weight of the heart was not recorded. All patients with a recorded diastolic blood pressure reading of 90 mm. of mercury or higher were considered to have hypertension. Most of the patients had several blood pressure readings recorded, and if at any one time a diastolic blood pressure reading of 90 mm. of mercury was obtained, we considered the patient to have hypertension and excluded his case from the study of hypertrophy. We do not maintain, however, that we have thereby eliminated all patients who may have had hypertension prior to the onset of hyperthyroidism. Furthermore, as hyperthyroidism sometimes causes a transient elevation of the diastolic blood pressure it is possible that some cases in which hypertension was not present have been excluded. An analysis of the remaining eighty-nine cases which consisted of sixty-nine cases of exophthalmic goiter and twenty cases of hyperfunctioning adenomatous goiter revealed the following:

1. In fifty-seven cases of exophthalmic goiter and sixteen cases of hyperfunctioning adenomatous goiter, a total of seventy-three cases (82 per cent), the hearts weighed less than 400 gm.

2. In eleven cases the heart weighed less than 250 gm.; in twenty cases it weighed between 250 and 300 gm., in forty-two cases between 300 and 400 gm., and in fifteen cases between 400 and 500 gm. In one case the heart weighed 530 gm.

3. When a comparison of the weight of the heart was made with Smith's standard maximal value for the usual weight of the patient prior to illness, it was found that in 49 per cent of the cases the actual weight of the heart exceeded the maximal standard value. It is highly probable that such hearts are actually hypertrophied. If the actual weight of the patient at the time of death was used as a basis for comparing the weight of the heart to the standard, it was found that in practically all instances the weight of the heart exceeded Smith's maximal values.

4. A study of the cases of seventeen patients aged less than thirty-

five years without hypertension or intrinsic disease of the heart showed that the heart weighed less than 400 gm. in sixteen (94 per cent) of the cases; in seven (41 per cent) of the cases the heart weighed between 300 and 400 gm., and in one case (6 per cent) it weighed more than 400 gm. Thirty-five per cent of the patients aged less than thirty-five years had cardiac weights exceeding Smith's maximal normal values.

5. There were only four patients whose cardiac weight was less than the normal minimal standard value. One of these patients was a girl aged fifteen years who had lost 48 per cent of her usual bodily weight. Another was a patient with mild hyperthyroidism of three months' duration, who died following a laparotomy done twenty-five days after thyroidectomy. The remaining two patients had lost respectively 37 and 44 per cent of their usual bodily weight.

6. In the eighty-nine cases under consideration there were sixty-six cases of exophthalmic goiter and twenty cases of hyperfunctioning adenomatous goiter.* These sixty-six cases of exophthalmic goiter could be separated into three groups: (1) thirty patients whose hearts might be considered to be hypertrophied, that is, the weight of the heart exceeded the maximal normal values by 20 gm. or more; (2) nineteen patients whose hearts might be considered as being normal or slightly hypertrophied, that is, the weight of the heart did not differ by more than 20 gm. from the maximal normal values, and (3) seventeen patients whose hearts weighed less than the maximal normal values by an amount exceeding 20 gm. A consideration of these three groups showed that the percentage of patients whose hearts exceeded the maximal normal values tended to increase in each succeeding decade, and that, conversely, the percentage of patients whose hearts weighed less than the standard tended to decrease in each succeeding decade. The percentage of patients whose hearts were approximately equal in weight to the standard varied independently of age. No constant correlation between the height of the basal metabolic rate and the weight of the heart could be found, although of nine patients whose basal metabolic rates were above +100 per cent, the weight of the heart exceeded the maximal standard in seven. It was also found that the majority of patients whose hearts weighed less than the standard or equaled it in weight had been ill for one year or less and that, conversely, the majority of patients whose hearts weighed more than the standard had been ill for much longer periods. These facts indicate that the duration of the hyperthyroidism is an important factor in the determination of the weight of the heart. A rough parallelism existed between the loss of bodily weight and the weight of the heart. Of the thirty patients whose cardiac weight exceeded the maximal normal standard, only three (10 per cent) had lost more than 30 per cent of the bodily weight, and of the seventeen

*Three cases of exophthalmic goiter could not be included because the usual weight of the patient prior to illness was not known.

patients whose cardiac weight was less than the maximal normal standard, eight (46 per cent) had lost more than 30 per cent of the bodily weight.

A consideration of the facts presented leads us to believe that in a given case of hyperthyroidism the weight of the heart at death will depend on the resultant of several factors, among which are: (1) the weight of the heart before the onset of hyperthyroidism; (2) the age of the patient; (3) the duration of hyperthyroidism; (4) the amount of excess work for each beat as the result of hyperthyroidism, and (5) the amount and rapidity of the loss of bodily weight. In a series of cases one would expect to find, depending on which factor predominated, cardiac weights ranging from subnormal values to values definitely indicative of hypertrophy.

CONGESTIVE HEART FAILURE

Congestive heart failure occurs as a manifestation of hyperthyroidism with such frequency that Moebius was led to believe: "Basedow patients suffer and die through their hearts." Since this dictum was formulated the pendulum has swung to the other extreme, so that now one frequently encounters statements to the effect that there is never failure of the heart in hyperthyroidism unless the heart has been diseased prior to the onset of hyperthyroidism. There probably is some truth in each of these attitudes, but there is reason to believe that neither is entirely correct.

Severe congestive heart failure manifested by edema of the lower extremities with ascites or hydrothorax occurred in twenty-seven cases (15 per cent) of the entire group of 178 cases under consideration. In nine of the cases of congestive failure no clinical or pathological evidence of hypertension or intrinsic cardiac disease was present, and it is probable that if the heart had been relieved of the burden of hyperthyroidism, health would have been restored to all of these patients, with the possible exception of one patient whose right auricle contained a ball thrombus.

In the remaining eighteen cases hypertension or intrinsic disease of the heart was present. However, in eight of these cases there was no clinical or pathological evidence to indicate that cardiac compensation and restoration of health would not have occurred if it had been possible to have controlled the hyperthyroidism. In the remaining ten cases the ultimate prognosis might have been questionable because of the presence of severe hypertension, nephritis or other cardiac disease even though thyroidectomy could have been performed successfully.

From the foregoing it is evident that of the twenty-seven cases of congestive heart failure restoration of health would probably have occurred in at least seventeen, if the hyperthyroidism could have been controlled.

It is unusual for congestive heart failure to appear during the course of hyperthyroidism in young patients. In this series of cases there were only two patients aged less than thirty-five years. One of them had hypertension and nephritis. The other, a man aged thirty-two years, had congestive heart failure, no cause for which other than hyperthyroidism was found. The weight of the heart at death of four patients with congestive failure was less than 300 gm., and of one patient it was only 205 gm. This patient was a woman aged forty-three years who had had exophthalmic goiter for seventeen months. She was admitted to hospital in a severe state of decompensation. On examination, edema of the legs, ascites and bilateral hydrothorax were revealed. The basal metabolic rate was +71 per cent. Auricular fibrillation was present. The blood pressure in millimeters of mercury was 162 systolic and 62 diastolic. An electrocardiographic tracing showed auricular fibrillation and an inversion of the T-waves in the derivations II and III. Under treatment the patient improved so that double ligation of the superior thyroid arteries could be performed, following which cardiac compensation was restored. She returned to the clinic three months later greatly improved. There was no evidence of the former decompensation except moderate edema of the legs. The cardiac rhythm was normal. Following thyroidectomy severe reaction occurred from which the patient died in less than twenty-four hours. At necropsy the right auricle and left ventricle were found to be markedly dilated, but the heart was otherwise normal. Undoubtedly there are many similar cases in which the patients do not die that are classified as cases of hyperthyroidism with independent disease of the heart because of the presence of congestive failure.

Auricular fibrillation occurred with increasing frequency in each decade in the 178 cases, and either auricular fibrillation or auricular flutter occurred in practically all of the cases of congestive heart failure. Clinically, one sees patients with hyperthyroidism who tolerate auricular fibrillation remarkably well. On the other hand, cardiac decompensation may occur in the course of hyperthyroidism when the auricles fibrillate so rapidly that a pulse deficit occurs; for example, the heart of the patient whose case history was just cited might not have been decompensated had the cardiac rhythm remained normal. In a study comprised only of fatal cases of hyperthyroidism it is impossible to evaluate auricular fibrillation as a factor in the production of congestive heart failure. In one of our cases congestive failure and death seemed to be the result primarily of a disturbance in cardiac rhythm. This patient was a woman, aged forty-three years, who had auricular flutter prior to thyroidectomy. After thyroidectomy normal rhythm was established. At the time of her dismissal from the clinic she appeared to be in good health. Apparently there was recurrence of the auricular flutter, for she returned to the clinic two months later with severe decompensation and

with an established auricular flutter. Death occurred shortly afterward. Post-mortem examination failed to disclose any intrinsic cardiac disease.

SUMMARY AND CONCLUSIONS

1. In eighty-nine fatal cases of hyperthyroidism, without evidence of hypertension or complicating disease of the heart, the weight of the heart in 49 per cent of the cases exceeded Smith's maximal standard values calculated on the basis of the patient's weight prior to illness.

2. The weight of the heart in a given case of hyperthyroidism depends on a number of factors, among which are: the weight of the heart prior to the onset of hyperthyroidism, the age of the patient, the duration of hyperthyroidism, malnutrition with its tendency to decrease the weight of the heart, and finally the amount of excess work placed on the heart as the result of hyperthyroidism.

3. In 178 fatal cases of hyperthyroidism severe congestive failure of the heart occurred in twenty-seven. Of these coronary sclerosis, hypertension, acute or chronic pericarditis, rheumatic endocarditis or syphilis were present in eighteen (67 per cent). In the remaining cases no cause for the congestive failure other than hyperthyroidism could be found.

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(For discussion, see page 149.)

STUDIES IN THYROID HEART DISEASE*

II. Angina Pectoris and Hyperthyroidism

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In A previous paper we[1] reported a series of cases of associated angina pectoris and hyperthyroidism. In that report we called attention to the fact that the association of angina pectoris and hyperthyroidism had been relatively little commented upon in the literature although known to occur. Since then, additional reports have appeared confirming the association of angina pectoris and hyperthyroidism. Levine[2] has noted the relief of anginal attacks after thyroidectomy. Haines and Kepler[3] in a series of 33 patients with angina pectoris and hyperthyroidism report improvement of the anginal symptoms in the majority of their subjects after thyroidectomy.

It must be remembered that there are many causes for chest pain and that not all substernal or precordial distress means angina pectoris. One must exclude the pain and distress of mitral stenosis, aortic stenosis, pericarditis, endocarditis, aortitis, aortic insufficiency, etc. This we have endeavored to do in our present report.

There is no reason why a patient with angina pectoris may not develop some other disease, and conversely why angina pectoris may not occur in the course of another illness. On the mere basis of chance therefore, angina pectoris could be associated with almost any other disease. If, however, certain conditions occur more commonly than others in association with angina pectoris, and if, particularly, the removal and the eradication of these conditions is usually followed by relief and improvement of the anginal syndrome, then it is only logical to believe that the association was something more than merely casual or accidental. We believe it indicates a probable "cause and effect" relationship, and it is in this sense that we used the word "association" in the title of our first paper.

Angina pectoris has been associated with a number of diseases. It has been reported in association with the anemias,[4, 5, 6] diabetes, tonsillitis and rheumatism, coronary disease and others. Syphilis, which was at one time believed to be a frequently associated factor in angina pectoris has been shown to be of very little significance. It is listed last in Kahn's[7] report of over a dozen associated diseases in a series of 82 patients with angina pectoris. Nevertheless, it is our practice to make a Wassermann test and rule out syphilis in all cases of angina pectoris particularly when it occurs in younger individuals. Angina pec-

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toris has also been associated with excessive smoking[8] and abdominal adhesions.[9]

In angina pectoris, male patients are in the majority while in hyperthyroidism, females have predominated. In the associated cases, females outnumber the males, five out of six in our previous series and seventeen out of thirty-three in Haines and Kepler's group. We are not certain why angina pectoris should be more prevalent in women with hyperthyroidism than in men. It may be a mere coincidence, or it may be that we see so many more women with hyperthyroidism than men, that complicating or associated conditions are therefore more likely to be also found in greater number among the female patients than among males.

FOLLOW-UP REPORT

In 1928 we reported six cases of associated angina pectoris and hyperthyroidism. Five of these had a subtotal thyroidectomy performed. Four of these were reported as having been relieved of their anginal pains for a period of from six to seventeen months at the time of our writing. The fifth patient was not improved and died a month after thyroidectomy. We have been able to follow up three of the surviving patients.

Mrs. I. H., aged fifty-nine years, had had typical attacks of angina pectoris for a number of years which had become especially more frequent, more severe, and more incapacitating in the two years prior to her admission to the hospital. A subtotal thyroidectomy was performed in January, 1929, for an exophthalmic goiter. She left the hospital nearly a month later after recovering from a postoperative bronchopneumonia. It is now over three years since her thyroidectomy. There have been no recurrences of any chest pain or distress to date. She is now able to walk in the cold and against a cold wind without any of the previous "severe grinding pain in the left chest and under the sternum" which often caused her to stop in her footsteps until the pain disappeared. The complete postoperative relief of anginal symptoms, which were becoming progressively more frequent and more severe, indicates, we believe, some relationship between the malfunctioning thyroid and the production of angina pectoris.

Mrs. A. B., aged fifty-nine years, suffered with angina pectoris for several years and an exophthalmic goiter which had become quite evident in the past year. These anginal pains were so pronounced that a surgeon in one of the hospitals dared do no more than a single polar ligation for the hyperthyroidism. This afforded no relief either for the chest pains or the hyperthyroidism, and the patient entered the Michael Reese Hospital several months later. On March 30, 1927, a subtotal thyroidectomy was done. For the next twelve months she was free of chest pains. In the latter part of 1928 and for a period of about six months she had mild infrequent substernal distress on effort. She then continued free of all anginal pains until November, 1931, when she had a sudden stroke (cerebral hemorrhage) while working in her kitchen at home and died 24 hours later without regaining consciousness. This case illustrates improvement of angina pectoris following thyroidectomy for an associated exophthalmic goiter. In addition, in this case, surgery was also followed by marked improvement of cardiac decompensation which was present for several years prior to thyroidectomy.

Mrs. A. J., aged sixty-two years, suffered with angina pectoris and an adenoma with hyperthyroidism for about seven months prior to her admission to Michael Reese Hospital, March 13, 1927. X-ray treatments to the thyroid failed to give relief. On March 29, 1927, after the usual preoperative preparation, a subtotal thyroidectomy was performed. We have seen this patient from time to time now over a period of 5 years. She is quite active for a woman of her years, and with the occasional exception of mild precordial discomfort following some pronounced nervous or emotional strain, she has had no recurrence of her severe anginal syndrome. This case illustrates improvement of angina pectoris following thyroidectomy for an adenoma with hyperthyroidism.

Report of new cases:

CASE 1.—Mrs. F. K. (A75342) housewife, aged forty-five years, had a thyroidectomy performed in June, 1926, for an adenoma with hyperthyroidism. She was not seen again until March, 1932. She stated then that following the thyroidectomy she felt well until two years ago. Since then she has been noting substernal pain coming after effort, on walking, particularly walking after a large meal or against a cold wind. The pain was also noticed following nervousness and excitement. The pain frequently radiated to left shoulder and arm and caused the patient to stop and rest until it disappeared. In addition, she had noted an enlargement in the region of the left lobe of the thyroid. Coincident with this she was becoming aware of increasing nervousness, weakness and insomnia.

Examination showed a pulse of 88 and a blood pressure of 210/100 mm. A firm, smooth nodule, the size of a hazelnut, was palpable in the left thyroid region. Two basal metabolism tests were 21.7 per cent above normal. Our impression was that this was a case of recurrent thyrotoxicosis with angina pectoris. The patient was put on Lugol's solution m. × t.i.d. p.c. She has now been under observation for one month. The chest pains have disappeared entirely. The relief of the anginal pains without any other restrictions or treatment is very suggestive. Surgical removal of the thyroid nodule is being considered.

CASE 2.—Mr. J. W., fifty-nine years old, tobacco merchant, seen in May, 1928 complained of pain in the chest for the past two years. This distress consisted of a severe pressing pain retrosternally coming on walking, stair climbing and after nervous excitation. The pain radiated at times to the right chest. Rest relieved the pain.

Examination showed: pulse 84; B.P. 190/110 mm.; Wassermann reaction, negative. Moderate exophthalmos; Von Graefe sign positive; thyroid negative to inspection and palpation. The heart was enlarged to the left and right and the second aortic tone was accentuated and booming. The liver dullness extended three fingers below the right costal arch but was not tender on pressure. Fluoroscopic and x-ray examination of the chest showed a non-pulsating mass the size of an orange in the superior mediastinum on the right side. The mass moved with deglutition. The trachea was moderately compressed and deviated to the left. Our impression was that this was a case of thyrotoxicosis (substernal thyroid) with angina pectoris.

A basal metabolism test made the next day was 7.6 per cent below normal. However, we continued to regard this as a case of hyperthyroidism. Following a series of x-ray treatments over the substernal mass in the next few months, his chest pains disappeared almost entirely and the substernal mass decreased in size. In November, 1931, his basal metabolism rate was 18.6 per cent above normal. He was then put on Lugol's solution m i to x B.I.D. in increasing doses. He has remained free of anginal symptoms up to the time of this report.

We believe this case is one of angina pectoris occurring in association with a sub-

sternal thyroid. Plummer[10] and Morris[11] have reported cases of hyperthyroidism with normal or lowered basal metabolic rates with improvement after thyroidectomy.

CASE 3.—Mr. S. K., married, merchant, was diagnosed as a thyrotoxic case in December, 1925, at the age of fifty-seven years, and was given several x-ray treatments over the thyroid region. When seen again in August, 1929, he complained of substernal discomfort in the past eight weeks. One week ago he experienced a sudden severe pain in the region of the precordium accompanied by a sense of impending death. Pain was relieved by nitroglycerin under the tongue. Two basal metabolic rates were +51.1 per cent and +38.5 per cent respectively. Diagnosis at this time was angina pectoris and thyrotoxicosis. A month later he again complained of increasing precordial pains associated with effort and worry. A basal metabolic rate now was 55.9 per cent above normal. Ten days later after the usual preoperative care, a subtotal thyroidectomy was performed. Patient left the hospital a month later after recovering from a postoperative right lower lobar pneumonia. It is now over two years since the thyroidectomy. He has continued feeling well to date and has returned to active duties as executive of a large concern.

We have had other patients illustrating the same association of angina pectoris and hyperthyroidism, with relief of the angina pains following the administration of iodine and thyroidectomy, but for our present purpose, these three case reports will, we believe, suffice.

DISCUSSION

In angina pectoris associated with hyperthyroidism we would suggest that the already accelerated heart, working at a constant disadvantage, is more susceptible to any sudden or increased demands made upon it by exertion, nervous influences, etc. Such a heart, if it be competent, responds to these demands without the appearance of any distress; if not competent, pain may follow. The occurrence of angina pectoris in individuals close to or over fifty years of age, rather than in younger, hyperthyroid patients, suggests that in the former the heart may already be the seat of some vascular or myocardial changes and that the added burden upon such a heart by an increased body metabolism results in the heart being unable to meet still further some sudden demands upon it, and cardiac pain results. In young hyperthyroid individuals, with the myocardium and vascular supply intact, the hyperthyroid heart is still able to meet increased demands, and no pain results. We believe this to be the more likely explanation for the occurrence of angina pain in older thyroid patients.

We do not feel that angina pectoris in hyperthyroidism represents a separate entity due to any specific effects of the thyroid gland, but rather that in these hearts there is already some underlying groundwork for the occurrence of angina pains in the presence of hyperthyroidism.

The practical importance of this report is the recognition that angina pectoris and hyperthyroidism may and do occur in association with each other. The possibility of an offending thyroid should be more often considered and looked for in cases of angina pectoris. In elderly women

especially should the possibility of an underlying thyroid disorder be ruled out in cases of angina pectoris.

We are of the opinion that angina pectoris in cases of hyperthyroidism is no contraindication to thyroidectomy. We believe rather that surgery is strongly indicated. In our experience these patients, after the proper preoperative treatment, tolerate subtotal thyroidectomy about as well as other cases of hyperthyroidism in the hands of a competent surgeon. The postoperative relief of the hyperthyroid and angina symptoms in most of the patients justify, in our opinion, the surgical steps taken.

SUMMARY

Attention is called to the association of angina pectoris and hyperthyroidism. We believe that thyroidectomy is not contraindicated in the presence of angina pectoris, and have found that in the majority of cases relief of the anginal symptoms followed the use of iodine and thyroidectomy. The exact mechanism of the production of angina pectoris in hyperthyroidism and the interrelationship between the two conditions are not clearly understood at this time. We believe, however, that in such patients the underlying groundwork for the anginal syndrome already exists, such as coronary sclerosis with or without occlusion, myocardial fibrosis, aortitis, etc., and that the toxic thyroid (hyperthyroidism) is the additional burden which precipitates an anginal attack.

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(For discussion, see page 151.)

THE INFLUENCE OF THYROID EXTRACT AND HYPERTHYROIDISM ON THE ELECTROCARDIOGRAM, WITH SPECIAL REFERENCE TO THE T-WAVES*

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PROOF of a definite relationship between an increased metabolic rate and the form of the T-wave of the electrocardiogram would be invaluable in differentiating Graves' disease from other clinical conditions which are accompanied by tachycardia. Such definite proof is still lacking, though a certain type of T-wave of large amplitude and rolling contour has been noted in many cases of hyperthyroidism, and has been called a "thyroid T-wave."

Hoffman[1] in 1914 was the first to call attention to the high T of electrocardiograms in hyperthyroidism. He believed that the height of the T-wave paralleled the rapidity of the pulse.

In 1918, Krumbhaar[2] corroborated these observations, but in the same year White and Aub[3] concluded that there is a very limited correlation between the rate of basal metabolism and the amplitude of the T-wave.

Pardee[4] observed an increased height of the T-wave in definitely toxic cases of hyperthyroidism. Lewis[5] stated that in thyrotoxicosis "except from the enhanced rate of beat and slight changes resulting therefrom, no definite alterations have been seen in the shape of the ventricular complex."

Willius[6] has studied a large series of cases of hyperthyroidism electrocardiographically and noted that the T-waves are frequently unusually prominent, especially in lead 2.

Hamburger,[7] in a series of cases, has reported the T-wave increased in height in several, but states that the increase is not uniform and has little, if any, relationship to the rate of the pulse.

Don and Langley[8] in 36 cases of toxic goiter concluded that the size of T bears no constant relationship to the metabolic rate or clinical condition of the patient.

To determine any specificity of changes in T-waves during thyrotoxicosis the records in 222 cases were examined. After eliminating such extrinsic factors (which are apt to alter the T-wave) as digitalis, iodine therapy and complicating heart disease, there remained but 16 records. In 4 of these the rolling contour of the T-waves is beautifully exhibited. (See Figs. 1 and 2.)

The characteristic thyroid T-waves differ from the ordinary T-wave in their individual and peculiar contour. (See Fig. 3.) There is not necessarily an increase in their width or height although frequently

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they are of unusual duration and amplitude. As Lewis[5] has stated that the changes of the T-wave in such patients are the consequence of an increase in the cardiac rate, electrocardiographic records of 25 cases exhibiting a sinus tachycardia from a variety of causes have been examined. None shows the high voltage or "rolling" T-waves which were seen in some of the cases of thyrotoxicosis. In addition, electrocardiographic records of 25 cases of neurocirculatory asthenia were studied, and much to our surprise T-waves quite similar to the so-called "thyroid T-waves"

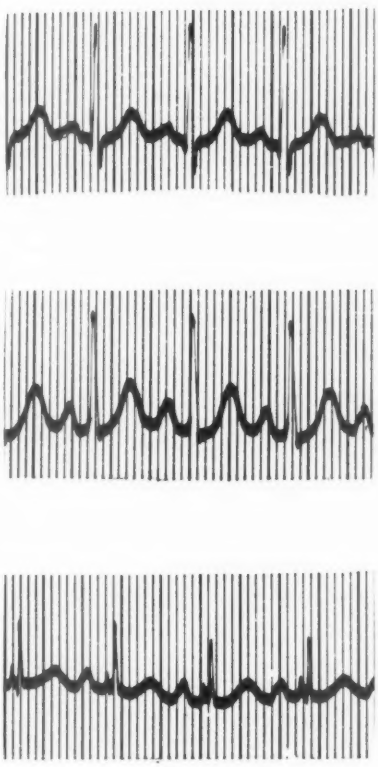

Fig. 1.

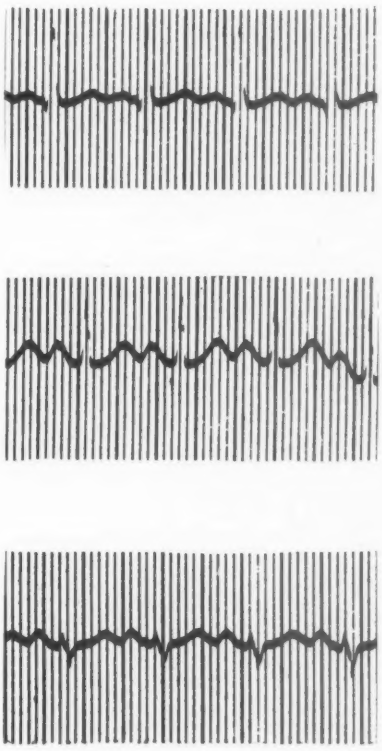

Fig. 2.

Figs. 1 and 2.—T-waves in hyperthyroidism illustrating the high voltage and rolling contour.

have been found in 5 and these in patients with a pulse rate of 90 or less. (Fig. 4.)

Because of the rather confusing results both in our clinical studies and in the literature pertaining to this subject, it occurred to us that the administration of thyroid extract to individuals without hyperthyroidism might be of interest. Five volunteers were selected and the records from 2 of the 5 cases are shown in Figs. 5, 6, 7 and 8. It should be mentioned that in Case 1 (Figs. 5 and 6), a patient with nephrosis, the basal metabolic rate was changed by medication from —30 per cent to

+25 per cent. This patient received 6 grains of thyroid extract daily for one month. In Case 2, a normal individual (Figs. 7 and 8), the control pulse rate was 80 and was increased to 130 by the administration

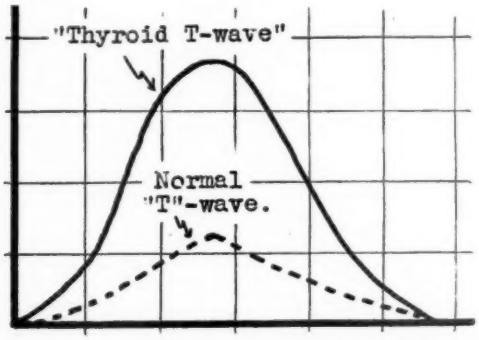

Fig. 3.—Diagram of "thyroid T-wave" (solid line) and normal T-wave (dotted line).

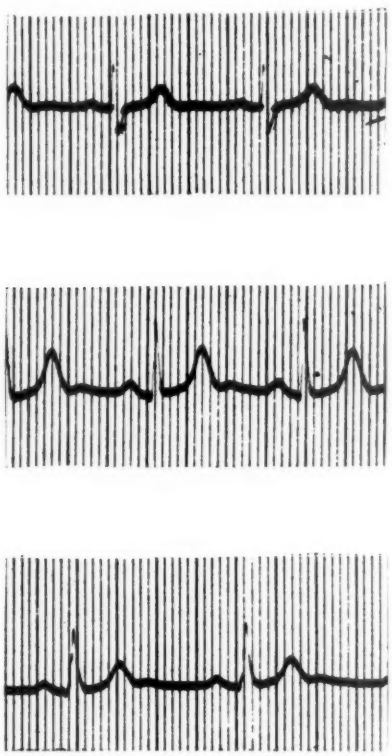

Fig. 4.—A T-wave in neurocirculatory asthenia simulating the thyroid T-wave.

of daily doses of 6 grains of thyroid extract for 2 weeks. In the remaining 3 cases there was an increase in the voltage of the T-waves but not to the same degree. Fig. 9 (the record of a patient with hyper-

thyroidism, a basal metabolic rate of +33 and pulse rate of 60) shows that the rate *per se* is not the specific factor which so remarkably influences the voltage and configuration of the T-waves.

As we were unwilling to administer toxic doses of thyroid extract to humans, it was decided to give large doses of this substance to normal dogs. In the first animal the cardiac rate in the control was 78 and the T-wave upright. Following the administration of thyroid extract, 20

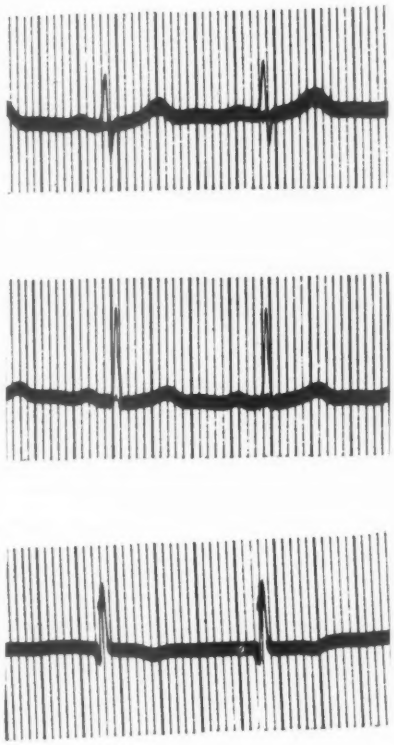

Fig. 5.

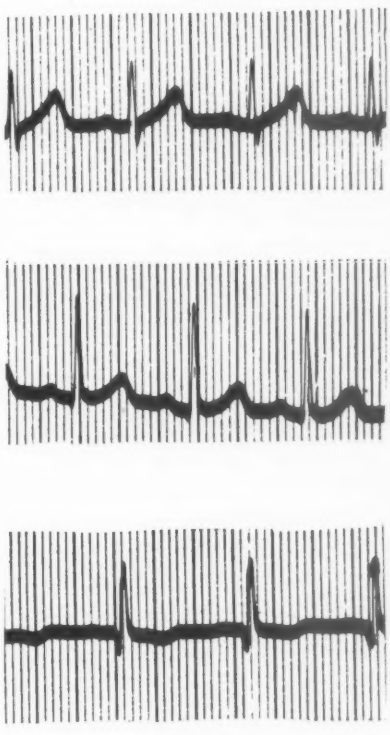

Fig. 6.

Figs. 5 and 6.—A case of nephrosis before and after thyroid medication.

grains daily for seventeen days, the rate increased to 120 and the T-waves became peaked.*

With a second animal both stellate ganglia were extirpated. Thyroid administration was then begun, 150 grains of thyroid extract being given in 33 days. One sees in the electrocardiograms that after operation the T-waves become negative and resemble in many ways those seen in cases of coronary occlusion, but this change is transient and in twenty-four

*We have been feeding 3 dogs with 20 grains of thyroid extract daily. In all the pulse rate attained a maximum in ten days and has subsequently been decreasing. The dogs are becoming increasingly irritable and are losing weight. The electrocardiographic and pathological findings will be reported later.

hours the electrocardiogram resembles the control record. During thyroid extract medication the T-waves again become negative and the rate progressively increases, reaching 120, after the dog had received 150 grains. At no time did the so-called thyroid T-waves appear in this dog or in any other dog in whom the T-waves were originally negative.

SUMMARY

It is apparent, therefore, that there has been no uniformity in the electrocardiographic findings in patients with thyrotoxicosis. The

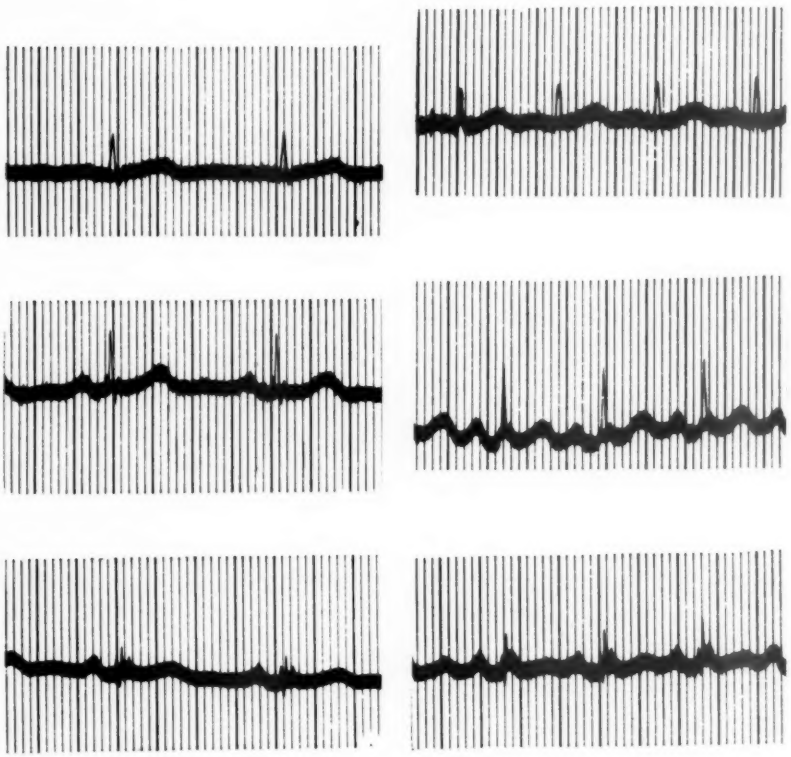

Fig. 7. Fig. 8.

Figs. 7 and 8.—Electrocardiogram of a normal individual before and after administration of 84 grains of thyroid extract in seventeen days.

"thyroid" T-waves seem to bear no relation to the pulse rate nor to the basal metabolic rate. Furthermore, there is no constancy in their occurrence. Patients with marked degrees of tachycardia may fail to show T-waves of high amplitude and, conversely, with a slow pulse rate they may be encountered. This would seem to eliminate the heart rate as a factor in determining the height of the T-waves. And similarly it appears that the basal metabolic rate can be shown to have no relation to the amplitude of the T-waves. Characteristic, so-called "thyroid"

T-waves have been found in our records of patients with thyrotoxicosis with metabolic rates as low as —32. Some other factor must be sought to explain their occurrence. This factor, we believe, is probably unrelated to the thyroid gland per se, since we have found similar T-waves in cases of neurocirculatory asthenia.

Since a high pulse pressure is common in thyrotoxicosis and is not infrequent in neurocirculatory asthenia, we are investigating its relation to the amplitude of the T-waves, but can express no opinion at the present time.

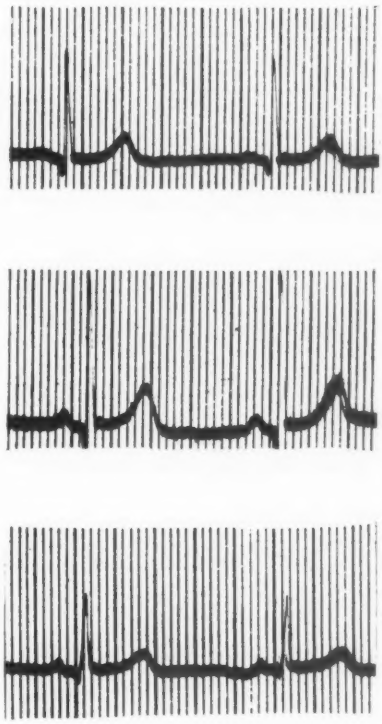

Fig. 9.—A case of hyperthyroidism, basal metabolic rate +33, pulse rate 60, illustrating a high voltage T-wave with low pulse rate.

CONCLUSIONS

1. The T-waves in the electrocardiogram of uncomplicated cases of thyrotoxicosis quite frequently are of unusually high voltage and of rolling contour.

2. These changes are not dependent upon the pulse rate or upon increased basal metabolic rate, and are not specific for thyrotoxicosis since they are seen also in neurocirculatory asthenia.

3. The administration of thyroid extract to normal individuals will produce comparable alterations in the human electrocardiogram.

4. In dogs the administration of large doses of thyroid extract causes tachycardia and increase in the voltage of the T-waves.

5. Removal of the stellate ganglia in one animal experiment did not prevent the development of tachycardia under thyroid medication.

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(For discussion, see page 151.)

AURICULAR FIBRILLATION IN GRAVES' DISEASE*

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ALTHOUGH the importance of the cardiac complications of Graves' disease† had long been recognized, auricular fibrillation, one of the most common and serious of these complications, received but meager notice prior to 1918. In that year Krumbhaar[1] called attention to its frequent occurrence in hyperthyroidism. Since 1923 many papers[2, 3, 4, 5, 6, 7, 8, 9, 10] have appeared in which the various aspects of auricular fibrillation as a complication of Graves' disease have been discussed. The purpose of the present report is to present a brief summary of the study of 108 cases of auricular fibrillation in Graves' disease observed by us between 1923 and 1927.

In addition to these 108 patients observed personally by us, there were many other cases in which auricular fibrillation was observed or suspected by other members of the hospital staff. It is estimated that approximately 15 per cent of the patients with Graves' disease in this clinic during these years had auricular fibrillation. In general, it may be stated that only the more seriously and critically ill patients, or those in whom the cardiac manifestations of the hyperthyroidism were most prominent were referred to us.

A general survey of this series of cases reveals the following facts. Of the 108 cases studied, 74 had toxic adenomatous goiter, and 34 had exophthalmic goiter. The patients in the adenomatous group were somewhat older than those in the exophthalmic group, the average age of the former being 54 years and of the latter 47 years. The average age for the entire series was 51.5 years. The average duration of the thyroid enlargement was much longer in the adenomatous group, being 19 years as compared with 3 years for the exophthalmic group. The average duration of the so-called "toxic symptoms," however, was 1.4 years in the former and 1.5 years in the latter; and of auricular fibrillation 1 year and 0.8 year, respectively. Of the 74 patients with adenomatous goiter 56, or 76 per cent, were females, while only 14, or 41 per cent, of the 34 patients with exophthalmic goiter were women. The basal metabolic rate before treatment was somewhat higher in the exophthalmic group than in the adenomatous, the averages being plus 53 per cent for the former, plus 46 per cent for the latter, and plus 48 per cent for both groups combined. The mortality also was distinctly higher in the

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†The term "Graves' disease" as used in this paper is synonymous with the terms "hyperthyroidism" and "toxic goiter," and includes "exophthalmic goiter" and so-called "toxic adenomatous goiter."

exophthalmic group, being 38 per cent as compared with 22 per cent for the adenomatous group and 27 per cent for the entire series of cases.* In spite of these dissimilarities between the two groups, there were no significant differences from the cardiac standpoint, so that for the purposes of this study the entire series may be considered as a whole. This is in agreement with the conclusions of Kerr and Hensel.[2]

High grade congestive *cardiac failure* was much less common than might be expected, occurring in only 17 per cent of these cases. A slight grade of failure occurred in 46 per cent, while 37 per cent showed none of the usual signs of congestive failure, although shortness of breath and palpitation were common symptoms. Only half of the patients who died had cardiac failure and some of these had pneumonia, hemorrhage and other complications, which probably were important factors in the fatal outcome.

Auricular fibrillation in Graves' disease is much more often *transient* or *paroxysmal* than that due to other causes. In this series 25 cases, or 23 per cent, were of this type. Of these, 5 had auricular fibrillation only during a rather stormy postoperative period. The patients with paroxysmal auricular fibrillation did not differ materially from those with chronic auricular fibrillation with respect to age, duration of symptoms, or basal metabolic rate. Quinidine stopped individual attacks of fibrillation in some of these patients, and in many it either prevented the occurrence of attacks or reduced their frequency, while in others it appeared to have little or no effect. Of these 25 patients, 19 had thyroidectomy and 15 survived the postoperative period. These were all relieved of their fibrillation with the exception of one who had only hemithyroidectomy, and whose attacks were temporarily stopped but returned 3 months after operation.

The cardiac manifestations of Graves' disease may dominate the clinical picture and obscure the underlying thyroid disorder. Indeed, auricular fibrillation, apparently due to Graves' disease may appear before there is a significant elevation of the basal metabolic rate or any evidence that the work of the heart has been increased, as illustrated by the following cases.

One was the case of a woman 47 years of age, who had attacks of paroxysmal auricular fibrillation for three years. For a long time careful study revealed no evidence of Graves' disease or of any organic heart condition which might have caused the attacks. The heart rate and blood pressure were normal between the attacks. Finally tremor, loss of weight, diarrhea appeared; still the basal metabolic rate was only plus 13 per cent. Thyroidectomy was performed and the patient was completely relieved of these symptoms and of the attacks of auricular fibrillation for a period of at least 5 years.

The other case was that of a man, 21 years of age, who had attacks of auricular flutter in the spring of 1925 and again in October, 1925. Careful examination re-

*This mortality is high by present standards. The reasons for this, we believe, are that the most seriously and critically ill patients were referred to us, and that the full benefits of iodine were not obtained in the earlier cases.

vealed no abnormality of the heart or of the thyroid gland which might have caused the attacks. The blood pressure and the heart rate were normal during the normal rhythm. The basal metabolic rate was minus 15 per cent and minus 17 per cent upon two occasions in November, 1925. In March, 1927, there appeared nervousness, tremor, sweating, and flushing, and the blood pressure was 160/95 mm.; still the basal metabolic rate was only plus 1 per cent. In May, 1927, the patient developed very severe exophthalmic goiter from which he recovered entirely after subtotal thyroidectomy. There have been no further attacks of flutter.

In these two cases there is strong presumptive evidence that the cardiac disturbances were due to Graves' disease, but appeared before the Graves' syndrome was fully developed and before there was any evidence that the work of the heart was materially increased. Thyroidectomy after the Graves' disease was fully developed resulted in complete cure, with cessation of the attacks of abnormal rhythm. Three somewhat similar cases have been reported by Hamilton.[9] Wishart[11] has also called attention to cases of this type. Other cases resembling these have recently been described by Morris.[12] Levine and Sturgis[6] and Parkinson and Campbell[13] have reported cases in which the cardiac manifestations were so prominent as to mask the underlying hyperthyroidism, even when the basal metabolic rate was elevated.

Digitalis is somewhat less effective in auricular fibrillation due to Graves' disease than in fibrillation due to other causes. On the average the amounts of the drug tolerated are larger, and the beneficial effects are less striking. Nearly all of our patients received a standardized tincture of digitalis, one cubic centimeter of which equalled one cat unit. It was given in doses of two cubic centimeters, three times daily, and was usually continued either until a satisfactory clinical response occurred or to the point of mild intoxication. The approximate tolerance could be estimated in 49 cases. If the average normal tolerance is 15 cat units per 100 pounds of body weight[14, 15] and the average normal rate of disappearance of the drug is 1.4 cat units per day[15, 16] (and this was in accord with the results obtained in patients with fibrillation not due to Graves' disease), then these 49 patients had a tolerance which was 134 per cent of the normal average. Four had a tolerance which was more than two and one-half times the average normal. Only one fell conspicuously below the average tolerance; she was a very obese woman of 63 years, with a basal metabolic rate of only plus 14 per cent, who developed nausea and ventricular rate of 64 after taking only 36 per cent of the theoretical digitalizing dose. Digitalization, carried out as described above, reduced the average ventricular rate in this group of patients from 119 to 90 per minute. The average basal metabolic rate of these patients was plus 48 per cent, the same as for the entire series of 108 cases. The response of some of these patients to the intravenous administration of ouabain or digifoline was determined and found to be on the whole less striking than that of patients with auricular fibrillation

not due to Graves' disease. In general it may be said that the patients with the higher basal metabolic rates have higher initial ventricular rates, tolerate larger amounts of digitalis, and show less ventricular slowing in response to digitalis. Exceptions to this rule, however, are common.

The most striking failures of digitalis to slow the ventricles were observed in the very toxic state which sometimes occurred shortly after thyroidectomy. While this state persisted large doses of digitalis given intravenously often failed to influence the heart perceptibly, and ventricular slowing occurred only after the extreme thyroid intoxication had passed off.

Some patients showed entirely satisfactory slowing of the heart by digitalis, and a few had slow ventricular rates before the administration of the drug. Most, but not all, of these were patients with relatively little elevation of the basal metabolic rate. Our experience in respect to digitalis is similar to that of Foster,[10] Sturgis,[17] and Grant,[18] and is contrary to that of Kerr and Hensel[2] and Hamilton.[9]

Following successful treatment of the underlying Graves' disease, recovery from auricular fibrillation with the return of normal rhythm is usually prompt and striking. Restitution of the heart to normal is often complete in every respect. Our experience suggests that, generally speaking, the most satisfactory treatment for the cardiac manifestations of Graves' disease is partial or subtotal thyroidectomy. Only 53 of the 68 patients operated upon survived. This is a mortality of 22 per cent, and, when compared with the almost negligible postoperative mortality in Graves' disease without auricular fibrillation, emphasizes the well-known fact that the presence of auricular fibrillation is accompanied by a material increase in the risk of thyroidectomy.[10, 19] Nevertheless the mortality was considerably higher in those who had other forms of treatment; 14 of the 40 patients, or 35 per cent, who did not have thyroidectomy, died. Some of these, of course, did not have thyroidectomy because it was thought they were in too serious a condition to withstand this operation. Furthermore, the degree of improvement is strongly in favor of surgical treatment, many of the patients who recovered from operation being restored to practically complete health while none of those who did not have thyroidectomy are known to have recovered completely.

Of the 53 patients who survived thyroidectomy 28, or 53 per cent, were completely relieved of fibrillation by operation alone. In only 7 of these did fibrillation persist for more than 2 weeks following operation. Of the other 21 patients, 13 had paroxysmal fibrillation which did not return after convalescence from operation. Two of the 28 patients failed to respond to quinidine after operation.

Of the remaining 25 patients, 14 were given quinidine which restored normal rhythm in 11, while the 3 in which quinidine failed, and the

11 others, who did not receive quinidine, continued to have auricular fibrillation and are not known to have returned to normal rhythm. All but one of the patients who failed to respond to quinidine developed toxic symptoms upon very small doses, so that the drug could not be given in adequate amounts. Most of the patients in this series who were given quinidine received the drug during the second or third postoperative week.

Six patients received quinidine preoperatively. In 3 of these normal rhythm was restored, but fibrillation returned in all during or following operation. Similar discouraging experiences with quinidine preoperatively have been reported by Sturgis,[17] Hamilton,[9] and others, while Foster[10] and Read[20] advocate the administration of quinidine before thyroidectomy when fibrillation is present.

Of the 40 patients who did not have thyroidectomy, 6 received quinidine, with restoration of normal rhythm in 4. Of the 34 who did not receive quinidine only 1 stopped fibrillating; in the others the auricular fibrillation persisted.

Our experience suggests that thyroidectomy is at present the best treatment for Graves' disease complicated by auricular fibrillation. We believe that in addition to the usual preparation for operation these patients should be fully digitalized. Soon after operation, within a few days or a few weeks, quinidine may be given to those who do not return to normal rhythm spontaneously. In this manner one may expect to restore normal rhythm in approximately 90 per cent of the patients recovering from operation. When the normal rhythm follows operation spontaneously or in response to quinidine therapy it is usually permanent, no doubt because the cause of the fibrillation has been removed. The mortality, although considerable, will be less than in other forms of treatment and the proportion of patients restored to practically normal health will be very high. There is no other type of chronic heart disease in which so nearly a complete recovery is possible. The frequent spontaneous return of normal rhythm after thyroidectomy has been emphasized by Krumbhaar,[1] Hamilton,[21] Sturgis,[17] Dunhill, Fraser, and Stott,[5] and Lahey.[22] The value of quinidine in those cases in which fibrillation persists after thyroidectomy has been stressed by Dunhill, Fraser, and Stott,[5] Lahey,[22] Hay,[23] Anderson,[24] and others.

Cardiac hypertrophy is seldom pronounced in Graves' disease. Cardiac enlargement when present is due chiefly to dilatation. In some of our patients the clinical signs of considerable cardiac enlargement were confirmed by roentgenological examination. In others, however, the great overactivity of the heart gave the impression of considerable enlargement when the x-ray films showed little or no increase in the heart's size. In many, however, there were no signs of enlargement clinically or by x-ray. Of the 29 patients who died, 13 came to autopsy. The average heart weight in these cases was 438 grams. In only two instances did

the heart weigh more than 500 grams; in each of these it weighed 530 grams, and one of these two patients had hypertension during life.

In some respects the cardiac disturbances of Graves' disease resemble those induced by the toxemia of an acute infection such as diphtheria or pneumonia, especially in respect to the frequency of transient or paroxysmal disturbances of the cardiac rhythm, and the almost complete return to normal after recovery from the underlying condition. The rarity of pronounced cardiac hypertrophy suggests the operation of other factors than overwork of the heart. Those cases in which the cardiac disturbances, presumably due to Graves' disease, occur before there is any evidence that the work of the heart has been increased lend further support to this view. In fully developed Graves' disease, however, the work of the heart is obviously increased to a significant extent and this is undoubtedly one of the important causes of the cardiac complications of this disease.[17, 20, 25] Difficult as it is to estimate the relative importance of the mechanical and the toxic factors, these observations suggest that the toxic factor is of considerable importance. Although this conclusion is contrary to the opinions of Hamilton,[9] Lahey[22] and others, it is in agreement with the views of Goodpasture[27] and Plummer.[28]

SUMMARY AND CONCLUSIONS

A study of 108 cases of auricular fibrillation in Graves' disease, observed between 1923 and 1927, is presented. The incidence of this complication in this clinic during those years was approximately 15 per cent.

The average age of the patients studied was 51.5 years. The average basal metabolic rate was plus 48 per cent before treatment; mild or severe cardiac failure was present in 63 per cent; and the mortality for the series was 27 per cent.

Auricular fibrillation due to Graves' disease is more likely to be transient or paroxysmal than that due to other causes. In this series 25 cases, or 23 per cent, were of this type.

The cardiac manifestations of Graves' disease may dominate the picture and obscure the underlying thyroid disorder; they may even antedate all other recognizable signs of the Graves' disease causing them. Two cases are cited in illustration of the latter observation.

Digitalis is less effective than in fibrillation not due to Graves' disease. The amounts tolerated are on the average larger and the beneficial effects are less pronounced. The digitalis tolerance could be estimated in 49 instances. In these the average tolerance was 134 per cent of the theoretical normal tolerance, and the effect of digitalization was to reduce the average ventricular rate from 119 to 90 per minute. In the very toxic states which sometimes followed operation large doses of digitalis intravenously did not influence the ventricular rate materially.

Following successful treatment of the underlying Graves' disease, recovery from fibrillation is often prompt and striking. Restitution of

the heart rhythm to normal is often complete. Thyroidectomy followed by the use of quinidine in those patients in which normal rhythm does not return spontaneously soon after operation may be expected to restore normal rhythm in approximately 90 per cent of the cases.

Cardiac hypertrophy is seldom pronounced. Enlargement, when present, is due chiefly to dilatation. The average weight of the hearts of 13 patients coming to autopsy was 438 grams. The two heaviest hearts weighed 530 grams each.

In some respects the cardiac disturbances of Graves' disease resemble those induced by the toxemia of an acute infection. Although it is difficult to estimate the relative importance of the increased work the heart must perform as compared to the toxic factor, the infrequency of hypertrophy and the character of the cardiac disturbances suggest that the latter is of great importance.

The writers desire to express their gratitude to Dr. F. A. Coller and to others of the Department of Surgery for the opportunity of observing some of the patients included in this study.

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(For discussion, see page 152.)

THE INCIDENCE OF AURICULAR FIBRILLATION AND RESULTS OF QUINIDINE THERAPY

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THIS report is based on a study of the patients from the surgical services of Dr. Crile and Dr. Dinsmore during my association at the Cleveland Clinic from 1923 to 1931. It includes 426 patients with auricular fibrillation who had a complete thyroidectomy, which permitted the study of final results. During the same period there were approximately 150 additional patients with hyperthyroidism and auricular fibrillation who, for one reason or another, never had a complete thyroidectomy and hence are not included in this report.

The incidence of auricular fibrillation in patients with hyperthyroidism has varied in different years from 6 per cent to 9 per cent, but during the year 1930 it was 8.3 per cent and in 1931 it was 8.9 per cent. I think these figures represent an accurate proportion. In 1928 only 5.87 per cent of patients with hyperthyroidism presented this heart complication. This was a year when there was an unusually large number of patients with hyperthyroidism and also an unusually large number with symptoms which had persisted for only short periods, in some for only one to three months, and in such a group, I think, one might expect a smaller incidence of auricular fibrillation.

The beginning of this period (1923) antedates the routine preoperative use of iodine as advocated by Plummer, and at that time ligation of thyroid arteries was being done in 60 per cent of the patients at the Cleveland Clinic. Following the institution of the routine use of iodine, it was found that ligation of the arteries was almost never necessary, and now it is done only occasionally. Lobectomy or thyroidectomy is usually done at the first operation; this has reduced the mortality considerably.

In a series of 2400 cases of hyperthyroidism, 18.5 per cent were in men and 81.5 per cent were in women. Of patients with auricular fibrillation and hyperthyroidism the ratio was 30 per cent males to 70 per cent females. This would seem to corroborate Means and Richardson's impression that men are inclined to have a more severe form of hyperthyroidism than women.

The oldest patient in this entire series was aged seventy-two and the youngest was eighteen years of age. The average age of the men was forty-nine years, and of the women fifty-one years. The average age for all patients with auricular fibrillation with diffuse hyperplastic goiter was 47.7 years and for those with adenomatous goiter was fifty years.

The patients with adenomatous goiters had been aware of their presence for an average of 14.5 years, while 60 per cent of those with diffuse hyperplasia were unaware of any thyroid enlargement. The other 40 per cent had known of a goiter for from three months to twenty years, and the average duration had been 2.8 years. The average estimated duration of hyperthyroidism in those patients with diffuse hyperplasia with auricular fibrillation was 2.5 years and in those with adenomatous goiter 2.3 years. This is in contrast with eight months and twelve months respectively in those with normal rhythm. Auricular fibrillation was present in several patients who appeared to have had hyperthyroidism for only one month.

Some form of focal infection was present in 50 per cent of those with auricular fibrillation, and in 32 per cent of those without fibrillation. Syphilis occurred in 1.7 per cent of the patients with fibrillation.

Signs of congestive failure were present in only 3.2 per cent of those with normal rhythm as compared with 30 to 60 per cent (different series) of those with auricular fibrillation. An enlarged heart as shown by roentgen ray was present in only 6 per cent of those with normal rhythm and in each instance was associated with a diastolic blood pressure of 100 or more. On the other hand, in 60 per cent of those with auricular fibrillation roentgenograms revealed enlarged hearts and only 8 per cent of these had a diastolic blood pressure higher than 100. There was a systolic murmur at the apex of the heart in 60 per cent of those with

TABLE I

THYROIDECTOMY AND QUINIDINE IN THE TREATMENT OF PATIENTS WITH AURICULAR FIBRILLATION

	75 SERIES 1	75 SERIES 2	185 SERIES 3	57 SERIES 4	34 SERIES 5
Regular after thyroidectomy	24 32%	45 60%	112 60.5%	26 45.7%	17 50%
Irregular after thyroidectomy	51 68%	30 40%	73 39.5%	31 54.3%	17 50%
Not treated with quinidine			57	7	0
Treated with quinidine		Late 3	Late 16	Prompt 23	Prompt 17
Regular after quinidine		2 66%	10 60%	22 96%	14 82%
Irregular after quinidine		1	6 40%	1 4%	3 18%
Regular after thyroidectomy and quinidine			122 66%	48 85-96%	31 91%

normal rhythm and in 46 per cent of those with auricular fibrillation. There was an associated mitral stenosis in 3 per cent of these cases.

The first series I reported included 75 surgical patients who had had a persistent auricular fibrillation; 60 per cent of the series showed heart failure, and in 20 per cent this had progressed so far that general anasarca was present. In spite of this complication, 97 per cent improved enough for ligation or lobectomy to be attempted. In 60 per cent of this group ligations preceded thyroidectomy. The mortality in this series was 15 per cent, and only 32 per cent acquired a normal heart rhythm after operation.

Quinidine was used in the treatment of three patients in this first series and was successful in two. Of those who continued to have fibrillation postoperatively, 55 per cent were very comfortable and able to lead active lives, and 45 per cent were forced to restrict their activities considerably. However, some of this restriction was necessary on account of other factors, such as arthritis or arteriosclerosis.

The average age for this first series was fifty-one years. In none of the patients in this group was the fibrillation transient; in many of them it had been present for years. The maximum duration was twenty years. This series does not, therefore, represent a true picture of auricular fibrillation in general, but does show the seriousness of long standing cases.

A second series of seventy-five patients subjected to operation on the thyroid included all who showed a definite fibrillation. In five patients this was transient, lasting from a few hours to a few days. Ten gave a history of paroxysmal attacks over a long period of time, and in sixty, there had been continuous fibrillation.

The average age of the patients in this series was forty-seven years, and the mortality after operation was 4 per cent. All in this series were operated upon after preoperative iodine therapy became a routine procedure.

Some degree of heart failure was present in 55 per cent of these cases. This was slight in 20 per cent, moderate in 20 per cent, and advanced in 15 per cent. Normal rhythm was established postoperatively in 60 per cent. Quinidine was used in six cases but was successful only in three.

In a third series of 185 cases, 60 per cent of the patients showed a normal rhythm following thyroidectomy. Sixteen patients in whom fibrillation persisted were given quinidine; of these, in ten a normal rhythm was reestablished. Of the entire group, the total number of cases in which normal rhythm was regained was 66 per cent:

Before 1929 quinidine had not been used until one week after operation as it had been felt that there would be more attendant danger. Also there were some patients who did not develop a spontaneous normal rhythm until one to four weeks after operation. However, by this time sufficient study had been made to establish the fact that not more than

60 per cent of patients would acquire a normal rhythm with thyroidectomy alone, and also that quinidine used late (two to three weeks after operation) would only raise this figure slightly. The patients usually left the hospital on the sixth or seventh day following thyroidectomy and were seldom accessible for treatment afterward. Only approximately 20 per cent were treated with quinidine on this basis.

In 1930 prompt quinidine therapy was made routine treatment. That is, all patients still having auricular fibrillation on the third day after operation were reported. They were given a test dose of quinidine that evening, and if no ill effects were encountered, they were started on the regular schedule the morning of the fourth day. This included 5 grains of quinidine sulphate every four hours, day and night for twenty-four hours, every three hours for the next twenty-four hours, and every two hours for the next forty-eight hours. The pulse was counted before each dose, and if it was regular no more of the drug was administered.

It was found that only 45 per cent of the patients had acquired a normal rhythm by the end of the third postoperative day. According to the earlier results, this means that 15 per cent of patients might be expected to acquire a spontaneous rhythm if allowed to go on without taking quinidine, but I know of no way to determine which patients would make this recovery.

During 1930 there were fifty-seven patients with auricular fibrillation who had complete thyroidectomy. Twenty-six, 45.7 per cent, developed a normal heart rhythm within three or four days following thyroidectomy without any quinidine. Of the remaining thirty-one patients, two died, making a mortality in the series of 3.5 per cent. Seven were unintentionally not treated with quinidine and continued to have auricular fibrillation. Twenty-three received quinidine according to the schedule outlined previously. Twenty-two of these, or 96 per cent, acquired a normal rhythm and one did not. This patient after her third dose of quinidine became dyspneic, flushed, nauseated, she perspired and experienced fear of death. Whether this was a quinidine reaction or pulmonary embolus could not be determined, but the patient refused further treatment and the fibrillation persisted.

During the study of this series no attention was paid to the rate of the heart or to the extent of digitalization, and I have not observed that complete digitalization prior to quinidine therapy offered any advantage in treatment. So far as I know, no patient in this series has had recurrence of the auricular fibrillation while under observation or afterward, and in no instance has the use of quinidine been continued after the establishment of normal rhythm.

During 1931 there were thirty-four patients with auricular fibrillation who had complete thyroidectomy. Seventeen of these, or 50 per cent, developed a normal rhythm without taking any quinidine.

Quinidine was used according to the regimen already outlined in

seventeen patients; the treatment was successful in fourteen, and unsuccessful in three. Thus, in the entire series, 91 per cent of the patients had a normal heart rhythm at the time they left the hospital and three patients or 9 per cent still had auricular fibrillation when they were dismissed. There were no deaths in this series. One of these three patients did not have a full course as he wished to get home as soon as possible, and the other two patients had had recurrent hyperthyroidism.

The results of treatment with quinidine were not quite so satisfactory in the 1931 series as in the 1930 series, but show that one can expect 90 per cent or more of all patients to acquire a normal rhythm if treated with quinidine shortly after operation. The ideal time for instituting the administration of quinidine is from the third to the sixth postoperative day. If treatment is postponed later than this, the percentage of failures increases considerably.

The question is frequently asked, "Will not these patients again develop auricular fibrillation under any stress?" I am sure the answer is "No." I have only very occasional reports of a patient who has developed a subsequent auricular fibrillation that has not been due to a recurrent hyperthyroidism, and will refer to one patient who illustrates very well how stable the heart may be. This patient was treated with quinidine and on the third day she developed a normal rhythm. A few months later she was operated upon for the removal of a large fibroid, which was followed by general peritonitis which caused her death. For several days the temperature had varied between 103° and 105.5°, and the pulse rate ranged from 130 to 160, but at no time was there any irregularity of the heart action.

One patient developed a recurrent auricular fibrillation while taking thyroid extract. She was forty-six years of age, and symptoms of hyperthyroidism had been present for two years before thyroidectomy. After operation she continued to be nervous, and had a basal metabolic rate of plus 23 per cent. She continued to have auricular fibrillation which digitalis did not completely control, though it did slow the ventricular rate from 130 to 100, per minute. It certainly appeared that this patient had a residual hyperthyroidism, but there was no thyroid tissue palpable. A course of Lugol's solution was given which did not affect the heart. She was then given quinidine and acquired a normal heart rhythm. With that her nervousness and other symptoms disappeared and she returned to work. About a year later she had a dry skin, was rather drowsy, and had other symptoms of hypothyroidism and was given thyroid extract. During its administration she developed auricular fibrillation which lasted about two weeks and stopped spontaneously.

One patient who had only a lobectomy was given quinidine on the fourth day after operation and acquired normal heart rhythm, but the next day auricular fibrillation reappeared. In my experience with quinidine therapy this case was analogous to those seen before the hyper-

thyroidism had been controlled by thyroidectomy. In cases where insufficient thyroid tissue is removed the rhythm may become normal after operation but seldom lasts permanently. No routine attempt has been made to produce a normal heart rhythm by the use of quinidine before operation, as this seldom persists, and the presence of auricular fibrillation with good compensation seems to be no contraindication to operation.

SUMMARY AND CONCLUSIONS

The presence of auricular fibrillation in patients with hyperthyroidism seems to depend on two factors: first, duration of symptoms, and second, the severity of the condition.

The mortality in such cases has been reduced greatly by the routine use of iodine before operation.

Approximately 45 per cent of patients acquire a normal rhythm within four days after thyroidectomy, and about 15 per cent more would develop a normal rhythm if allowed to go untreated, but there is no way of knowing which ones they would be.

The remaining 40 per cent would continue to have an abnormal rhythm indefinitely if not treated with quinidine.

In order to obtain the optimum results with quinidine, it must be used from the third to the sixth day following thyroidectomy, and success can be anticipated in from 90 to 96 per cent of the cases. If treatment is delayed longer than this, the percentage of failures increases considerably.

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(For discussion, see page 154.)

STUDIES IN THYROID HEART DISEASE*

The Value of Ergotamine in Hyperthyroidism and Its Effect on the Electrocardiogram

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THIS report is a clinical one and represents our experience and impression as to the use or value of ergotamine in hyperthyroidism, and the influence of ergotamine on the human electrocardiogram in these cases. Our interest in this drug was aroused by the relatively numerous reports of its use in hyperthyroidism abroad and because the drug was being increasingly recommended to the American physician by its manufacturer for use in similar cases. Accordingly, we were able to obtain a supply of the drug from the Sandoz Company for our studies.

The use of ergot in hyperthyroidism is not a new thing. Nearly twenty years ago Forchheimer[1] reported that he had used a combination of quinin and ergotin over a period of many years in Graves' disease. Forchheimer observed improvement in the tachycardia, tremor, and decrease in size of the thyroid gland under this treatment. In addition to stating that he obtained a great percentage of complete recoveries, he also recommended the use of quinin-ergotin as a preoperative measure to get the patients in condition for surgery.

About 10 years ago, Stoll[2] isolated the principal alkaloid of ergot. This was called ergotamine tartrate at the time but later came to be known also as gynergen. The two terms will be used here interchangeably. After its isolation, ergotamine came to be extensively used in place of ergot, as the former lacked some of the drawbacks of ergot itself. Today ergotamine or gynergen is supplied in tablets of 1 mg. each for oral administration and in ampules of ½ mg. each for hypodermic and intravenous use. Because it is generally recognized that there is an associated increased activity of the sympathetics in Basedow's disease, the use of ergot and ergotamine, which is known to have, or is thought to have, a depressing action on the sympathetics, naturally suggested itself as a means of relief. Accordingly, we find that ergotamine has been widely used in some European countries for this purpose. In our country, apparently, the drug has been relatively little used in goiter cases, judging from the scarcity of reports in the literature.

Among the earliest reports on the use of gynergen in hyperthyroidism is that of Adlersberg and Porges[3] published in 1924. They report a series of 22 cases treated over a period of one and one-half years. They

*From the Thyroid and Cardio-Vascular Groups, Michael Reese Hospital.
Aided by the Frederick K. Babson Fund and the Emil and Fannie Wedeles Fund of the Michael Reese Hospital for the Study of Diseases of the Heart and Circulation.

gave the drug subcutaneously 0.5 c.c. to 1 c.c. twice daily over a period of 1 to 3 weeks and then a week's period of rest. These authors divide their case results into three groups. Group I, consisting of 15 cases showing marked improvement subjectively and objectively, in tremor, tachycardia, exophthalmos, weight curve and basal metabolic rate. Group II, 4 cases with moderate improvement, and 3 cases in Group III showing no appreciable improvement. Their experience was that in the improved cases, recurrences took place 8 to 12 weeks after ergotamine was stopped, so that the medication had to be resumed with the reappearance of symptoms. They concluded at the time that ergotamine did not constitute a cure. In a latter follow-up report[4] of 13 of these 22 patients, they report nearly complete cure of the cases.

Marine[5] and his associates employed ergotamine to evaluate its effect on the heat production of normal and thyroidectomized rabbits. They employed the drug in doses of ⅛, ¼, and ½ mg. subcutaneously, using 0.9 per cent saline solution subcutaneously for control purposes. They report a striking fall in the heat production within one hour, the fall being proportional to the amount of ergotamine used. After thyroidectomy, employing ¼ mg. ergotamine in these rabbits, the heat production was again found lowered but to a less extent than in normal animals.

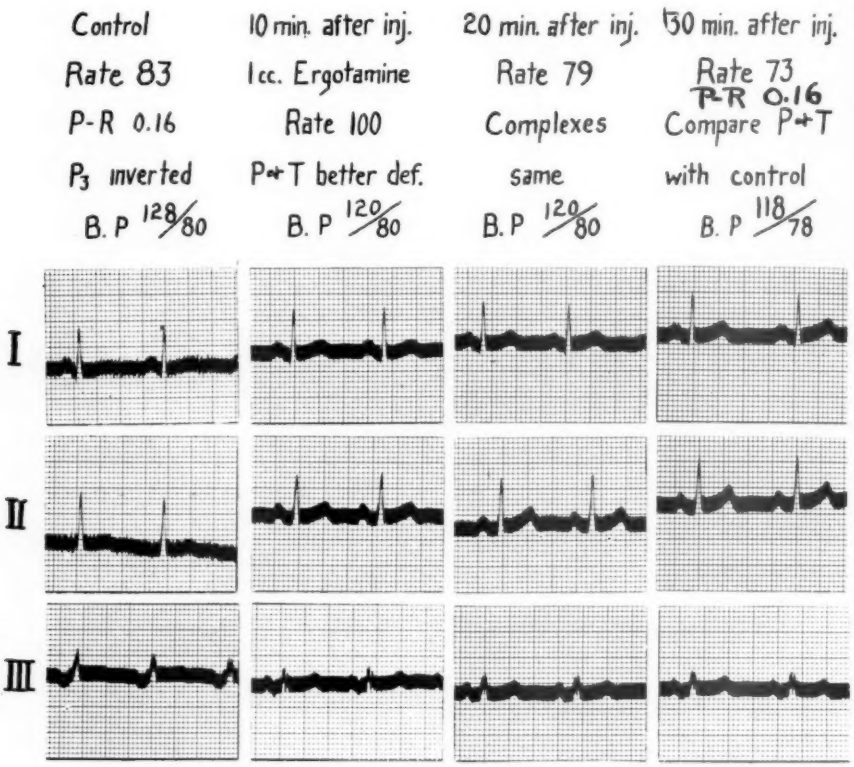
Youmans and Trimble,[6] who probably have done more work with ergotamine than anybody else in the country, used 0.25 mg. intravenously in normal trained dogs to test the effect of ergotamine on the oxygen consumption. They found that only 2 dogs showed a slight decrease in the O_2 consumption in the first hourly period while nearly all the others showed a rise, greatest usually in the first hour and decreasing to almost level limits at the end of the third hour. The giving of atropine (0.3 mg. or 0.4 mg.) before or after ergotamine injection did not influence the effect of gynergen on the oxygen consumption.

Employing nine normal human subjects, Youmans and Trimble[7] used 0.5 mg. ergotamine subcutaneously to test the effect of the drug on the basal metabolism. They found a slight elevation of the basal metabolic rate in three subjects at the end of three hours, while the others showed a variable drop (maximum 9 per cent) at some time after the injection but no greater variation than seen in control readings over the same period of time. In another series of 3 patients (normals) they gave 1 mg. ergotamine t.i.d. over a period of 8 days and found no change in the basal metabolic rates.

The same workers[8] in determining the effect of ergotamine on the heart rate in normal dogs employed 0.25 to 0.5 mg. of the drug intravenously. They found this to cause a sudden and marked slowing of the heart. Injection of 0.05 mg. atropine per Kg. entirely abolished this effect of ergotamine in slowing the heart. They concluded that ergotamine therefore produced its slowing action by a sensitizing or stimulating action on the vagus mechanism. In dogs with vagi cut, however, the injection of ergotamine still caused a slowing of the heart

but relatively much less than in intact dogs. During the course of this particular experiment, electrocardiographic studies showed no changes aside from slowing of the sinus rhythm.

In 1928, Merke and Eisner[9] employed gynergen to determine its effect on the human electrocardiogram in Basedow's disease. Using 1 c.c.



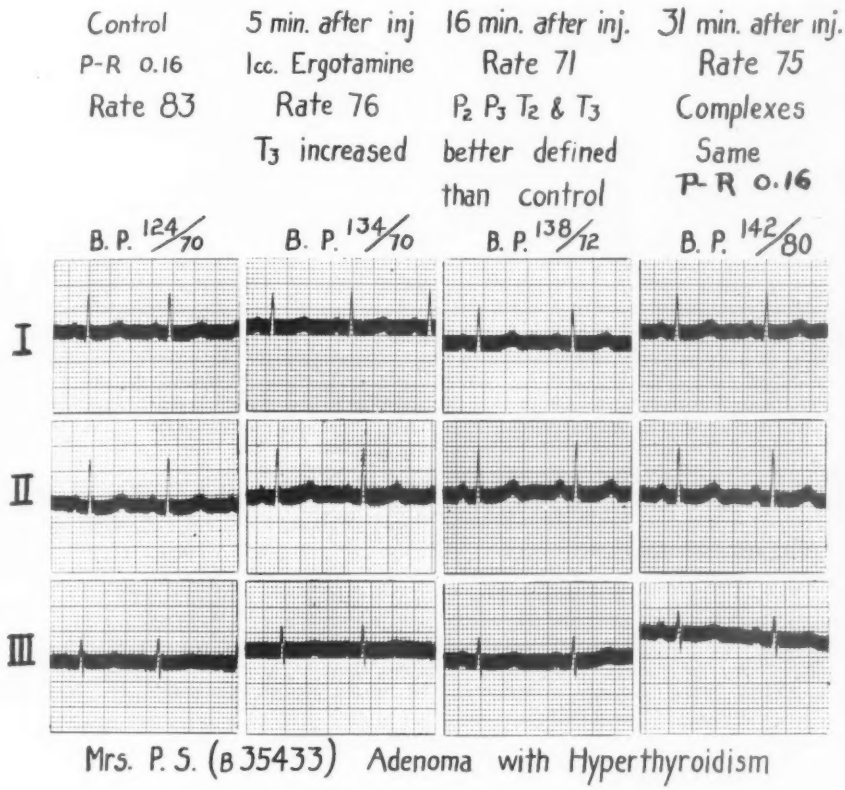
gynergen intramuscularly in a series of cases and taking curves 10 and 20 minutes after injection they found the following:

P-R interval prolonged.
R-R interval prolonged.
P-wave decreased in height in nearly all instances.
T-wave decreased in majority of cases.
R-wave decreased in majority of cases.

PERSONAL EXPERIENCES

Our series consists of six patients, 5 females and 1 male ranging in age from thirty-one to sixty-four years. Five of these had thyrotoxicosis of various degree and severity. The sixth had a nontoxic adenoma with pressure symptoms. Four of our group were given ergotamine

orally or hypodermically over different periods of time and their general, as well as their metabolic, response was noted. All six patients were given also 1 c.c. (0.5 mg.) of ergotamine subcutaneously and the changes in the electrocardiogram noted at approximately ten, twenty, and thirty-minute intervals after the injection.



CASE REPORTS*

CASE 1.—Mrs. M. B. (B36701), thirty-five years old; diagnosis exophthalmic goiter.

Metabolic Studies

Date	*B. M. R.*	*Pulse*	*Remarks*
4/14/31	+39.	80 80	No medication. First Reading.
4/17/31	+34.1	80	No medication.
4/22/31	+28.7	80	After receiving gynergen ½ c.c. "H" B.I.D. since 4/17/31.
4/29/31	+19.1	84	Gynergen ½ c.c. B.I.D. plus gynergen tab. q.i.d. since 4/22/31.
5/ 1/31	+13.6	84	Gynergen ½ c.c. B.I.D. plus gynergen tab. q.i.d. since 4/22/31.
5/ 6/31	Thyroidectomy		On Lugol's m. × t.i.d. since 5/1/31.
5/12/31	+21.5	88	

*Details of four of the six cases studied are given here.

CASE 2.—Mrs. P. S. (35433), married, aged forty-six years; diagnosis exophthalmic goiter; diabetes mellitus.

Date	*B. M. R.*	*Pulse*	*Remarks*
3/ 9/31	+43.2	78	No medication. First reading.
3/10/31	+26.2	72	No medication.
3/12/31	+25.6	76	Insulin therapy started.
3/18/31	+31.4	72	No medication except insulin.
3/23/31	+24.9	74	No medication except insulin.
3/25/31	+33.9	72	No medication except insulin.
3/28/31	+34.8	82	No medication except insulin.
4/ 7/31	+28.4	72	Lugol's m. × t.i.d. and ergotamine ½ c.c. B.I.D. started 4/2/31.
4/13/31	+15.9	68	On Lugol's and ergotamine since 4/2/31.
4/16/31			Subtotal thyroidectomy.
4/22/31	+ 2.5	68	One week after thyroidectomy.

CASE 3.—Mrs. A. C. (B35604), married, aged forty-five years; diagnosis adenomatous goiter with hyperthyroidism; mitral insufficiency; diabetes mellitus.

Date	*B. M. R.*	*Pulse*	*Remarks*
3/12/31	+62.7	100	No medication, first reading, not satisfactory.
3/16/31	+43.1	88	No medication.
3/18/31	+39.8	84	No medication.
3/23/31	+51.	76	No medication.
3/25/31	+46.8	72	No medication.
3/28/31	+52.5	68	No medication.
4/ 7/31	+46.9	80	On ergotamine ½ c.c. B.I.D. since 4/3/31.
4/13/31	+55.7	78	On ergotamine ½ c.c. B.I.D. since 4/3/31 and continued to 4/16/31 inc.
4/17/31	+40.9	92	On Lugol's m. × t.i.d. and Tab. ergotamine t.i.d. since 4/14/31.
4/22/31	+32.5	84	On Lugol's m. × t.i.d. (Gynergen tablet stopped 4/20/31.)
4/27/31	+45.9	100	On Lugol's m. × t.i.d.
5/ 5/31	+50.3	88	On Lugol's m. × t.i.d.
5/ 8/31	+ 9.3	80	On Lugol's m. × t.i.d.
5/11/31	+10.1	80	On Lugol's m. × t.i.d.
5/13/31			Thyroidectomy.
5/19/31	+18.7		

CASE 4.—Mrs. L. L. (B36257), widow, sixty-four years old; diagnosis recurrent thyrotoxicosis; bleeding duodenal ulcer; generalized arteriosclerosis; arteriosclerotic heart; cardiac hypertrophy; mitral insufficiency.

Date	*B. M. R.*	*Pulse*	*Remarks*
4/ 6/31	+30.8	96	No medication.
4/13/31	+40.6	84	No medication.
4/ 2/31	+30.7	72	Patient received 4 injections of ½ c.c. ergotamine between April 17 and 19. Drug discontinued when patient complained of marked palpitation, nervousness and severe abdominal pains and cramps.
5/ 2/31	+36.7	80	On Blaud's mass.
5/12/31	+30.2	76	On Lugol's m. × t.i.d. p.c. from May 3 to 7 when further Lugol's was refused by the patient.

We wish to state here that we realize that the number of our case determinations are relatively few owing to conditions at the time beyond

our control. During the course of administration of ergotamine, all but one case, with a complicating recurrent bleeding duodenal ulcer, stated they were improved. This improvement consisted of lessened nervousness and irritability, decreased palpitation, decreased tachycardia, and a feeling of increased strength. It must of course be realized that these patients were all at complete bed rest during this time and due account of this factor must be taken into consideration in evaluation of this drug as well as any other under similar conditions. However, we feel that too much stress or value should not be placed on the bed resting phase as being in a large medical ward among the sick, ailing and complaining patients cannot be said to be very conducive to the improvement or recovery of a thyrotoxic patient. No ergot poisoning was experienced in our series.

Incidentally during this time we employed ergotamine in a case of paroxysmal tachycardia of nonthyroid origin, which failed to respond to the usual measures for relief, and which was controlled by the subcutaneous injection of the drug. In another case of tachycardia in an old rheumatic heart, the heart rate was not slowed after the oral administration of gynergen—one tablet 3 times daily over a period of 3 to 4 weeks. In still another case of tachycardia of unknown source and without any other cardiac involvement and without evidence of hyperthyroidism, slowing of the heart rate was not obtained after several weeks of the drug by mouth. This is rather interesting in view of the slowing of the heart rate in goiter cases.

The electrocardiographic responses to ergotamine are more interesting and definite. After a control electrocardiogram, pulse rate, and blood pressure determinations, serial electrocardiograms were taken at approximately 10, 20 and 30 minute intervals following the subcutaneous injection of 1 c.c. gynergen. In addition, pulse rate and blood pressure readings were made every few minutes during this half hour period of observation. Likewise any new subjective symptoms which the patient experienced during this period were recorded. The electrocardiographic changes occur rather promptly and consist chiefly of a slowing of the heart rate, increased amplitude of the T-wave in most instances and particularly in Lead III, and the abolishing of the peripheral tremors present in some cases in the control electrocardiogram. The P-wave was increased in three cases, and decreased in two. In one case of thyrotoxicosis and auricular fibrillation, the electrocardiogram showed no changes in the complexes after the administration of ergotamine subcutaneously. The P-R interval was increased in two cases, and unchanged in the others.

The cause or causes for the P- and T-wave changes in this series offer an interesting field for speculation. The increase in the T-wave after the employment of a drug supposedly beneficial in hyperthyroidism is further very interesting in view of the report of a decrease in the T-wave under iodine medication and after thyroidectomy as reported previously

by ourselves.[10] It is to be noted here also, that the greatest changes occur in the third lead, which lead has always been considered as the most sensitive and labile of the three leads.

SUMMARY AND CONCLUSIONS

1. Four patients with hyperthyroidism were given ergotamine orally or hypodermically. One case showed an increased basal metabolic rate after 10 days; one showed a decrease in 14 days, one a decrease in 2 days, and the fourth case in which Lugol's had been combined with ergotamine a decrease in 11 days.

2. As a result of our experience we conclude that ergotamine, in the dosage and mode of administration employed is not as effective as Lugol's solution in reducing the basal metabolic rate. Neither do we feel that the drug can be called a "cure" for thyrotoxicosis. It does contribute to the subjective improvement of the patient but no more than does the use of Lugol's solution.

3. The tachycardia of hyperthyroidism is generally favorably influenced by ergotamine. The same drug when used in two cases of tachycardia not of thyroid origin, failed to produce a slowing of the heart rate.

4. Subcutaneous injection of ergotamine in the majority of instances causes a fairly prompt change in the electrocardiogram, consisting chiefly of a slowing of the heart rate and an increase in height of the T-wave. In two of the six patients it produced a prolongation of the P-R interval. It likewise causes in most cases of hyperthyroidism an increase in the systolic and diastolic blood pressure, persisting at least one-half hour after its administration.

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(For discussion, see page 154.)

Society Transactions

AMERICAN HEART ASSOCIATION, 1932

THE eighth annual scientific session of the American Heart Association was held at the Roosevelt Hotel, New Orleans, La., on May 10, 1932, with Dr. Harold E. B. Pardee as the presiding officer.

DR. PARDEE.—Today's presentation represents the second attempt on the part of the Committee for the Coordination of Investigation* to provide a comprehensive study of various phases of cardiovascular disease. By way of introduction to this symposium, it seems proper to point out the objectives which the Committee had in mind when selecting the subject. It was hoped to present a fairly complete picture of the cardiac disturbances, both physiological and pathological, which result from an abnormal functioning of the thyroid gland. It was hoped also to focus attention upon those points which were in dispute and especially upon those which seemed most ready for solution.

In the past, studies of the pathological features of the hearts of those with thyroid disease have frequently been unsatisfactory because of the difficulty in deciding what was due to the direct influence of the gland and what to a complicating factor. First, the coincident presence of arteriosclerosis of the coronary arteries has been a great source of confusion, and it seems that changes due to this have often been wrongly considered as an effect of thyroid disease. Second, auricular fibrillation, from its tendency to produce a rapid heart rate, can give rise to cardiac insufficiency and this in its turn to cardiac enlargement of myocardial fibrosis or possibly other changes. Obviously if such abnormalities result from heart failure, they cannot properly be considered as an effect of thyroid dysfunction upon the heart. It has been suggested that the prolonged cardiac overactivity which is known to result from hyperthyroidism might give rise to premature coronary arteriosclerosis, and it was hoped that we might be able to reach a decision as to whether or not such premature sclerosis occurs.

There has been no doubt but that thyroid disturbances lead to disturbances of cardiac function. The rate and rhythm of the heart and the blood pressure are evidently affected, but it is not yet definitely established whether the cardiac functional capacity is diminished by the uncomplicated influence of thyroid dysfunction. Auricular fibrillation, if permanent and associated with a rapid ventricular rate, is quite capable of causing serious cardiac insufficiency. The arteriosclerotic changes in the coronary arteries which appear normally after the fourth decade can also give rise to cardiac insufficiency. It is difficult in a patient who has either of these complicating conditions clearly to discern the influence of thyroid dysfunction upon the heart. We must try to separate the influence of the thyroid from whichever of these complications may be present, or better yet to select for study cases from which both can be excluded.

On the experimental side there is much to be learned about the effects upon the heart's function and structure produced by the administration of thyroxin and of thyroid gland. The heart after thyroidectomy has been little studied, either as to functional or structural changes. Finally the question of the influence of a simple nontoxic adenoma should be settled. Does this condition cause physiological and

*Edward P. Carter, Cary Eggleston, George R. Herrmann, William J. Kerr, Edward B. Krumbhaar, H. M. Marvin, Fred M. Smith, Paul D. White, Frank N. Wilson, Harold E. B. Pardee, Chairman.

pathological changes in the heart such as have been associated with under- or over-activity of the thyroid, or does it not? Each one of the contributors to this symposium has attempted to answer one or more of these questions and to investigate such other phases of the subject as have seemed important to them. From my preliminary correspondence with the authors who will address you today, I feel quite certain that by the end of this program they will have presented us with a much clearer picture of thyroid heart disease than exists at present.

The papers comprising the program of the meeting are published in this issue.

PROGRAM

The Mechanism of Adjustment of the Circulation in Hyperthyroidism (Thyrotoxicosis). Wallace M. Yater, M.D., Washington, D. C. (See p. 1.)

Cardiac Histopathology in Thyroid Disease. Carl V. Weller, M.D., R. C. Wanstrom, M.D., Harold Gordon, M.D., and J. C. Bugher, M.D., Ann Arbor, Mich. (See p. 8.)

A Study of the Heart in Hyperthyroidism. Geoffrey Rake, M.B., and Donald McEachern, M.D., Baltimore, Md. (See p. 19.)

The Signs and Symptoms of Heart Changes in Toxic Goiter. A Clinical Study of 148 Cases. Clough Turrill Burnett, M.D., and Edgar Durbin, M.D., Denver, Colo. (See p. 29.)

Cardiovascular Symptomatology in Exophthalmic Goiter. Jacob Lerman, M.D., and J. H. Means, M.D., Boston, Mass. (See p. 55.)

The Heart in Hyperthyroidism. E. Cowles Andrus, M.D., Baltimore, Md. (See p. 66.)

Cardiac Status After Prolonged Thyrotoxicosis. J. Marion Read, M.D., San Francisco, Cal. (See p. 84.)

Myxedema Heart. George Fahr, M.D., Minneapolis, Minn. (See p. 91.)

Congestive Heart Failure and Hypertrophy in Hyperthyroidism: A Clinical and Pathological Study of 178 Fatal Cases. E. J. Kepler, M.D., and A. R. Barnes, M.D., Rochester, Minn. (See p. 102.)

Studies in Thyroid Heart Disease, Angina Pectoris and Hyperthyroidism. Morris W. Lev, M.D., and Walter W. Hamburger, M.D., Chicago, Ill. (See p. 109.)

Experimental Observations Upon Hearts of Thyroxinized Animals. E. Cowles Andrus, M.D., and Donald McEachern, M.D., Baltimore, Md.

The Influence of Thyroid Extract and Hyperthyroidism on the Electrocardiogram, With Special Reference to the T-Waves. Johnson McGuire, M.D., and Margaret Foulger, M.D., Cincinnati, Ohio. (See p. 114.)

Cardiac Dilatation in Toxic Goiter: A Study of the Changes in the Size and Shape of the Heart Before and After Treatment. O. J. Menard, M.D., and Lewis M. Hurxthal, M.D., Boston, Mass.

ABSTRACT

Teleroentgenograms were made in one hundred and fifteen cases of toxic goiter, before, during, and after treatment. Comparisons of the films were made by superimposing one plate upon another. Changes in the chest, diaphragm, and so forth were given due consideration in deciding upon changes in heart size. Marked reduction in the size of the heart shadow was found after treatment, particularly in cases with auricular fibrillation and congestive failure. Relief of congestive failure alone caused a reduction in the size of the shadow, while a change from auricular fibrillation to normal rhythm produced a reduction in size in some cases.

The heart shadow became smaller after operation in a few cases with normal rhythm and without evidence of congestive failure. In about 50 per cent of those with normal rhythm and with evidence of congestive failure, there was a smaller shadow after relief of hyperthyroidism. Larger heart shadows after treatment were seen in a few cases and these were usually associated with coincident heart disease, excessive gain in weight, or occasionally unknown causes.

The shape of the heart was studied, and a prominence of the pulmonary artery was noted more particularly in toxic goiter cases than in nontoxic goiter cases. Slight to moderate degrees of ventricular hypertrophy were found particularly in cases of long duration, but gross cardiac enlargement was usually associated with coincident cardiovascular disease.

Auricular Fibrillation in Graves' Disease. Paul S. Barker, M.D.; Anne L. Bohning, M.D.; and Frank N. Wilson, M.D.; Ann Arbor, Mich. (See p. 121.)

The Incidence of Auricular Fibrillation and Results of Quinidine Therapy. John P. Anderson, M.D., Cleveland, Ohio. (See p. 128.)

The Value of Ergotamine in Hyperthyroidism and Its Effect on the Electrocardiogram. Morris W. Lev, M.D., and Walter W. Hamburger, M.D., Chicago, Ill. (See p. 134.)

READ BY TITLE

The Heart in Hyperthyroidism: An Experimental Study. Frank R. Menne, M.D.; Roger H. Keane, A.B.; Robert T. Henry, A.B.; and Noble W. Jones, M.D., Portland, Ore. (See p. 75.)

A Clinical Study of Goiter in the Pacific Northwest, With Special Reference to the State of the Heart. Noble W. Jones, M.D., Dean B. Seabrook, M.D., and Frank R. Menne, M.D., Portland, Ore. (See p. 41.)

The Heart Rate During Sleep in Graves' Disease and in Neurogenic Sinus Tachycardia. Ernst P. Boas, M.D., New York, N. Y. (See p. 24.)

The Heart in Thyroid Disease: Electrocardiographic and Orthodiagraphic Studies Before and After Thyroidectomy. Edward Rose, M.D.; Alexander Margolies, M.D.; and Francis C. Wood, M.D., Philadelphia, Pa.

(A preliminary report of this paper was read by title at the New Orleans meeting. The final report will be published later.)

DISCUSSION

Discussion of paper of Dr. Wallace M. Yater. (See p. 1.)

Dr. John J. Sampson, San Francisco, Calif.—There is additional evidence on this subject which was presented by J. K. Lewis and W. Dock, published in the Journal of Physiology, April issue of this year. Their work was designed to show the direct influence of thyroxin on the metabolism of heart muscle. They used a rat heart-lung preparation to determine the metabolism of the heart muscle in a normal animal and in an animal thyroxinized. They found that the direct measurement of the metabolism of the heart muscle was no greater than would be expected from the increased rate. The action of the thyroxin, they stated, is to increase the heart rate, and no increase in metabolism of the heart muscle occurred, greater than expected per gram per beat.

Discussion of paper of Drs. Carl V. Weller, R. C. Wanstrom, J. C. Bugher, and H. Gordon. (See p. 8.)

Dr. Harold E. B. Pardee, New York, N. Y.—I should like to ask Dr. Bugher if there were any special clinical features about the cases in which special pathological findings were observed, especially if cardiac insufficiency was present.

Dr. John J. Sampson, San Francisco, Calif.—Did the studies carried out at autopsy reveal anything peculiar in other organs than the heart, especially pancreas, kidney or skeletal muscles?

Dr. Wallace M. Yater, Washington, D. C.—A similar change is seen in rabbit hearts. Rabbits which have been injected with thyroxin are more susceptible to infection and also show unusual lesions after chloroform poisoning. They very readily develop focal necrosis throughout the heart and other lesions, which indicates that the myocardium in hyperthyroidism is less able than normally to cope with infection and poisons.

Dr. J. C. Bugher, Ann Arbor, Mich.—With regard to the special clinical features, the majority of these cases died primarily of pneumonia and other infections. In the exophthalmic goiter series, about the same number. Two-thirds of the cases of the combined exophthalmic goiter and adenomatous goiter series died with an attendant purulent infection of some kind, such as pneumonia or appendicitis. A number of them had tuberculosis. In general, a very complex and very far-reaching picture was presented from the standpoint of the full pathology of the cases.

Several of the deaths were ascribed to myocardial failure. Since the series goes back as far as 1896, it is possible that if these were diagnosed in the light of present knowledge, there might be changes in that opinion.

Of the seven cases showing cellular infiltrations in the myocardium, four had had auricular fibrillation and died of myocardial failure; another one of the earlier cases died of "acute cardiac dilatation"; a sixth died of cardiac failure in a thyroid crisis; the last case was one of lymphatic leucemia with the exophthalmic goiter secondary in importance. The four cases in which the cellular infiltrations were chiefly epicardial included two with auricular fibrillation, one of which died of myocardial failure.

With regard to the involvement of other organs in these cases, the chief organ involvement in the exophthalmic goiter series was the liver. Dr. Weller has reported the rather high incidence of what appears to be a nonspecific hepatitis in which there is heavy round-cell infiltration associated with some fibroblastic proliferation.

The other organs do not appear to show such distinctive inflammatory infiltrations, but there is very constantly in these exophthalmic goiter cases and in most of the adenomatous goiter individuals a hypoplastic cardiovascular state, associated with a hyperplastic lymphoid tissue.

The comment on the work on rabbits was very instructive. Goodpasture and a number of other workers have also called attention to this as a possible interpretation of such lesions occurring in the myocardium of human beings. We are not at all opposed to any such theory, although it does not necessarily follow from our investigative work. However, it is a reasonable interpretation of the association of these myocardial lesions with exophthalmic goiter.

Discussion of papers of Drs. Clough T. Burnett and Edgar Durbin (see p. 29); of Drs. Jacob Lerman and J. S. Means (see p. 55); and of Dr. E. Cowles Andrus (see p. 66).

Dr. George Herrmann, Galveston, Tex.—The point that Dr. Andrus made with relation to previous heart damage as a factor determining thyroid heart disease seems to be of some significance. Dr. J. A. Alvarez, who is studying the general heart condition at the Charity Hospital from 1926 to 1931, found himself in agreement with Dr. E. H. Schwab, who is studying the same question in Galveston. Both observed a considerable frequency and an early onset of heart complications in the thyrotoxic negro. In the study in Galveston it is striking that with a similar type of disorder the negroes have heart failure much earlier in life than do the whites. This observation is in line with some of Dr. Schwab's earlier studies which showed that the colored patient with hypertension developed heart failure earlier than did the

white. Dr. Schwab has suggested that the reason for the negro patient's earlier failure is the poor cardiovascular soil upon which the goiter reacts. He believes that the poor cardiovascular soil is a product of the recent civilization of the negro who has been forced to change his mode and especially his tempo of living. Dr. Schwab has gone back to the origin of the American negro and has found that the tendency to cardiovascular disease is not so great. At any rate in many of the negroes the age of thyroid heart disease is much under forty.

I wish to take issue with the statement of Dr. Lerman as to the possibility of carrying on with active exophthalmic goiter for many years without any cardiac manifestations. In my experience it is a distinct rarity for a patient with marked hyperthyroidism to have it for ten or twenty years without developing some organic myocardial disturbance. I still believe that the cardiac part of the exophthalmic goiter is a most important one and that the patient who has a perfectly normal myocardium before and after is quite an exception. We should have a statement as to the cause of death in the patients here considered to show the relative importance of cardiac failure in contrast to the other causes of death in these patients.

Dr. E. J. Kepler, Rochester, Minn.—I would like to ask Dr. Andrus if there were any patients in his series with congestive failure without persistent auricular fibrillation.

Dr. Louis F. Bishop, Jr., New York, N. Y.—I should like to call attention to the number of patients in whom Dr. Burnett found dizziness as a symptom. It is well known that a very rapid heart or a very slow heart may affect the blood supply to the brain with resultant dizziness, amounting in some cases to syncope. I was particularly interested to note that he found this symptom without any evidence of associated arteriosclerosis.

Dr. Wallace M. Yater, Washington, D. C.—This work is exceedingly interesting to me inasmuch as I have been doing the same kind of work independently of Dr. Andrus' group. He has worked in Baltimore and I have been working in Washington, only forty miles apart, and neither of us, apparently, was for a long time aware of the other's work. Our results have been practically identical in the main. The problems are multiple and difficult of solution. Of course, in the first place no one knows exactly what hyperthyroidism is. No one knows completely even what the function of the thyroid gland is. Why we should need a gland in the body to step our metabolism up 40 per cent is a mystery. When something happens to make the amount of thyroxin greater or less in the tissues, all tissues are affected in the same relative degree. The heart naturally is affected the same as other tissues of the body.

Theoretically what would be the effect of the increased rate of metabolism in the parenchyma of the only pulsating organ of the body? As I see it, there would be two main effects. First, there should be an increased irritability, which means tachycardia. The degree of tachycardia would depend mainly upon the amount of thyroxin in the myocardium, but would also depend to some extent upon the type of individual in whom the hyperthyroidism existed, whether sympatheticotonic or vagotonic, since there still exists a certain amount of nerve control. The other effect on the pulsating organ would be an increase in tone, with a corresponding increase in the force of the heartbeat. If the heart to begin with were hypotonic, there would be more increase in tone than in rate, a well known physiological principle. In either case, however, the resultant of these two main effects would be a considerable increase in minute volume output of the heart. Inasmuch as there is no physiological mechanism which controls the output of the heart in hyperthyroidism, the increased output is, therefore, largely a coincidence. It is easy for me to understand that the heart does more work than it normally should because it is a pulsating organ and in this condition lacks physiological control.

In regard to the work of Dr. McEachern with reference to the oxygen consump-

tion of strips of auricular muscle one should not place too much emphasis upon the results of this type of experiment, because such strips are doing practically no work.

In reference to the failure of the heart in hyperthyroidism, there are undoubtedly two main factors which act to bring about the failure. The first is age, with its natural diminution of cardiac reserve, and the second is general malnutrition, which naturally reduces the ability of any organ to carry on its work.

Dr. Harold E. B. Pardee, New York, N. Y.—I noticed there were some experiments which included observations of the effect of thyroid itself and also of thyroxin. I wonder if you have found any significant difference in the action of these two substances.

Dr. E. Cowles Andrus, Baltimore, Md.—All these animals received thyroxin or thyroid extract by mouth over relatively long periods of time, from ten days to two weeks. It is much easier to demonstrate the effect of thyroxin in this way than with the single large dose. It appears certain that thyroxin exerts no immediate effect in vitro. We were unable, in any experiments, to induce any significant reaction in isolated hearts by the addition of thyroxin directly to the perfusion fluid or to the bath in which the auricles were immersed. It is apparently true that noticeable reaction takes place only after a period of from twenty-four to thirty-six hours. After that the characteristic results appear and tend to persist for ten days to two weeks, unless the dose is repeated.

No quantitative differences were observed between the action of thyroxin and of thyroid gland substance.

Dr. Clough T. Burnett, Denver, Colo.—A question was asked as to the incidence of congestive heart failure and established auricular fibrillation. We found congestive heart failure in four cases in which there was no demonstrated fibrillation at any time. Negroes did not play a part in our series. I think there were only three in the entire group. I think perhaps the greatest trouble we had was in the determination of the duration of symptoms. How long have these patients had this trouble before they came in? How long has there been an effect on the heart? This is something which is sometimes very difficult to obtain in studying a record after six or seven years and with no contact with the patient.

Dr. Jacob Lerman, Boston, Mass.—As mentioned before, male patients complain very little. That, to us, is a prominent feature of the disease. These male patients may have had the disease for many years but do not come to the clinic until someone calls their attention to it.

Two years ago it was pointed out by Vanden Berg before the American Association for the Study of Goiter that patients often date the onset of their disease a year or less back, but that on questioning them after they are cured one finds their symptoms may actually date back ten or more years. Consequently the duration of the disease is difficult to determine.

Dr. E. Cowles Andrus, Baltimore, Md.—To answer the question concerning the incidence of fibrillation in connection with congestive failure, we had twenty cases in which there was normal rhythm and congestive failure, but many of those had paroxysms of fibrillation lasting from two to, in one case, sixteen hours. The duration of symptoms, I should agree, is very, very difficult to determine. I am prepared to believe that in the series we have reported it was greater, in the majority of instances, than was recorded.

Discussion of paper of Dr. George Fahr. (See p. 91.)

Dr. Jacob Lerman, Boston, Mass.—A week ago Dr. Means and I reported on a series of thirty patients with myxedema seen in Boston who had roentgen ray measurements of the heart taken before and after treatment. Our results are as follows: In fourteen cases the transverse diameter of the heart shrank 2 to 7 cm., and in six more it shrank 1 to 2 cm. The shrinkage of the heart was proportional to the

degree of enlargement. It is interesting to note that the time for the maximum shrinkage to take place was three to four months. Only one of the patients showed frank congestive failure.

Dr. J. Marion Read, San Francisco, Calif.—I should like to ask Dr. Fahr if he considers some other factor is operative to produce congestive failure in these patients with myxedema. I believe I can speak for most of those present that we frequently see myxedema patients even with metabolic rates as low as minus 30 who do not show evidence of myocardial decompensation. I have not yet seen a patient who fits Dr. Fahr's description of the "myxedema heart," although I have been looking for one ever since the publication of his first paper on this subject. I do not doubt that such a clinical picture exists, but I wonder if there isn't some complicating factor operating in these patients to produce the cardiac failure.

Dr. David W. Carter, Jr., Dallas, Tex.—I am surprised to hear Dr. Fahr say that there was only one patient in his series who developed anginal pain following treatment with thyroid substance. Our experience has been that it occurs more frequently than this in our series of patients of about the same age.

Dr. Bayard Holmes, Chicago, Ill.—The same condition prevails in beriberi. We see severe cases of beriberi with marked enlargement and dilatation of the heart, and as soon as they are put on a proper diet the size of the heart decreases just as with thyroid in these myxedema cases.

Dr. William D. Reid, Boston, Mass.—Did the abnormal electrocardiograms and roentgen findings always occur together, or sometimes was there a disagreement?

Dr. George Herrmann, Galveston, Tex.—I should like to ask Dr. Fahr what the relative hemoglobin concentration or the red blood cell counts showed in these hypothyroid cases that had the most extreme type of cardiac dilatation and edema and also what the blood serum protein levels were during the edema and after its disappearance.

Dr. Clough T. Burnett, Denver, Colo.—In the case of the anginal pain, did that pain appear before the reduction in the size of the heart?

Dr. E. J. Kepler, Rochester, Minn.—I would like to ask Dr. Fahr if an increase in the protein of the diet produced any change in the condition of the patients.

Dr. A. G. Sullivan, Hot Springs, Ark.—Did Dr. Fahr note the presence of arrhythmia in any of his cases; also does he believe that the increase in diameter of the cardiac shadow is due wholly to dilatation or may it not be due in part at least to a loss of cardiac muscle tone, causing the heart to assume a more transverse position on the diaphragm?

Dr. John P. Anderson, Cleveland, O.—One woman had a myxedema apparently dating back for 50 years and although she was taking thyroid extract regularly, her metabolism was still 33 per cent below normal. She had a marked secondary anemia and angina pectoris, but her heart border by x-ray was normal.

It is possible that the question of cardiac hypertrophy depends on the degree of myxedema.

Dr. Harold E. B. Pardee, New York, N. Y.—I should like to have you bring out how plain the signs of myxedema are in these patients at the time they present themselves with cardiac involvement.

Dr. George Fahr, Minneapolis, Minn.—Before I answer the questions which have been asked of me, I want to make a general statement, namely that because the characteristic symptoms of myxedema are usually so striking, the symptoms of heart failure may become wholly submerged, and it is frequently only when the physician is looking for symptoms and signs of heart failure that he will pick them up in his myxedema cases. I will begin the discussion by answering Dr. Lerman. His statistics on the transverse diameter of the heart in myxedema just about agree with mine. I think 65 per cent of our hearts showed a dilatation in the transverse diam-

eter. If we go back to the physiology of heart muscle, to the work of Otto Frank done about 1896 and to that of Starling of about 1912, we see that the work performed by the heart is a function of the length of the heart muscle fibers. In other words, if you give a ventricle an increased amount of work to do, it can do it only when it dilates or when the muscle fibers lengthen. And as a corollary to this, when you make the heart muscle hypodynamic, in order for the hypodynamic heart to perform the same amount of mechanical work, the heart has to dilate or its muscle fibers must stretch before it is capable of performing this amount of mechanical work. This means that the very earliest sign of the hypodynamic condition of the heart muscle is dilatation. Therefore the moment you are sure that 60-65 per cent of your Massachusetts General Hospital cases of myxedema showed a definite dilatation, I think you have to agree that you have evidence of the onset of the condition of heart failure. Signs of congestive heart failure may not yet have shown up, but ultimately they are going to do so. In a study of the heart in hypertension I have seen it time and time again that the heart first dilates a little and may keep on dilating for a number of years before definite symptoms of congestive heart failure appear.

I think the next question, and a very pertinent one, was asked by Dr. Herrmann. It is one I should have taken up more fully in my paper, but in my hurry to get through I forgot about it. This concerns the amount of hemoglobin and the red cell count in these cases. As you know, when the red blood cell count drops, the viscosity of the blood drops with it and if the mean pressure stays approximately the same, the minute volume of the heart must increase proportionately to the decrease in viscosity. As Dr. Ronzoni and I showed many years ago, in cases of severe anemia the minute volume may increase more than 100 per cent and therefore with this lowering of the red count, we get a tremendous increase in the work of the heart. Moreover when the red count is lowered very far, it is possible that under reduced velocity of circulation a condition of mild anoxemia might result. In our cases of myxedema the red count varied between three and one-half million and four and one-half million. This decrease in the cell count would lead at the best to only a 10 to 25 per cent increase in work of the heart provided the mean blood pressure remained the same. Of course this does not mean a 10 to 25 per cent increase in the work of the normal heart, but it means a 10 to 25 per cent increase in the work of a myxedema heart. As you very well know, the minute volume in myxedema is very much reduced so that the work of the heart is also very much reduced in myxedema. In the study of our cases we have seen the dilatation of the heart go down to normal and symptoms of congestive heart failure recede at the same time that the red blood cell count remained practically the same as it was before we gave thyroid extract; so I do not think that secondary anemia is an important factor in the production of heart failure in myxedema. The other question of Dr. Herrmann relating to the proteins of the blood in myxedema was a very pertinent one. I have been investigating the proteins of the blood and the colloid osmotic pressure in relation to edema formation for a number of years, and I have some information on this factor in myxedema. One of our cases of myxedema heart also had a marked lowering of serum albumin and the osmotic pressure of the plasma colloids so that this was undoubtedly a factor in the formation of edema in her case. In her case, dilatation of the heart receded and passive congestion of the liver and dyspnea disappeared before the plasma proteins returned to normal. In one other case where I have investigated the lowering of the serum albumin, it has been very slight and in consequence the lowering of the osmotic pressure of the plasma colloids was undoubtedly very slight and therefore this could, at the best, be only a very slight factor in the production of edema. Moreover, the heart failure symptoms had disappeared before the plasma proteins were back completely to normal, showing that this factor is probably of very slight importance.

There was a question about "frank congestive heart failure" by Dr. Lerman. I cannot explain why he got only one case of frank congestive heart failure in thirty cases of myxedema, unless he is speaking of a very advanced degree.

One of those who entered into the discussion talked about minus basal rates, apparently as synonymous with myxedema. I want to emphasize very vigorously that a minus thirty basal rate doesn't necessarily mean myxedema or hypothyroidism. Anyone who has a large experience with a group of girls on a university campus who have high I.Q.'s, fast mental reaction time, and who often lead in their classes, will know that a certain percentage of them have a rate of minus thirty or thereabouts. There is no reason to believe that these are cases of either myxedema or hypothyroidism beause they have not the symptoms of myxedema. I am inclined to believe, although I have no very good proof of it, that this minus rate has to do with some disturbance in the pituitary gland function. For me, the outstanding symptoms in myxedema are those of the central nervous system, and our studies have shown that the I.Q.'s go down very low and the reaction time slows up very decidedly. Also there is definite loss of memory in cases of myxedema. But in these young ladies with negative rates, these factors of central nervous disturbance are not present.

To two gentlemen who asked me about cases of myxedema heart with angina pectoris—I have seen only one case with angina pectoris. But in the literature you will find that there are many cases of myxedema with angina pectoris. In some of these cases the symptoms of angina pectoris disappear on thyroid treatment, but in others the angina pectoris increases on thyroid medication.

Dr. Pardee asked me a question about the myxedema symptoms. In those cases where we had the severest cases of heart failure, the myxedema symptoms were outstanding. They answered questions very slowly; their I.Q.'s as measured by our university psychologist were very low; their reaction time was tremendously slowed down; they had the characteristic puffy eyelids and the narrowed eye-slits. They had dry and scaly skin usually, rather than the thick and myxedematous type of skin. The symptoms were very marked in those cases with severe cardiac symptoms and a very marked dilatation of the heart. All of these cases had their myxedema for periods of time from anywhere from three to six or eight years. My youngest patient, a girl of nineteen, with a very moderate degree of heart failure, had had her symptoms of myxedema for a year or less. Only one of our cases had a definite thyroiditis with a hard woody gland. The young lady above mentioned had had some pain in her neck a year prior to the onset of symptoms. I couldn't say whether that was a thyroiditis or not.

In answer to Dr. Read concerning the correlation between dilatation of the heart and the electrocardiographic changes: if you mean do we always find the characteristic electrocardiographic changes when we find dilatation of the heart, then I would say yes. But if you have a patient who has been on thyroid extract for a long period and you then take him off the thyroid medication, you will find that the electrocardiographic changes sometimes come on a few months earlier than the marked dilatation and congestive heart failure symptoms. I mentioned that we had three cases of true myxedema in which we had no symptoms of a congestive heart failure and no dilatation of the heart; yet in all these cases the electrocardiogram shows a flat T. I haven't called these cases myxedema heart despite the fact that the electrocardiogram shows changes in the mechanism of the heart.

Discussion of paper by Drs. E. J. Kepler and A. R. Barnes. (See p. 102.)

Dr. George Fahr, Minneapolis, Minn.—Dr. Kepler, I want to be absolutely certain about this: Did you find that if you equated the heart weight to the body weight in all these cases of exophthalmic goiter or hyperthyroidism with adenoma the heart weight ratio was higher than the normal?

Dr. Wallace M. Yater, Washington, D. C.—In connection with the subject of hypertrophy, it is very interesting to note that the degree of hypertrophy in hyperthyroidism is slight when compared to that which occurs in hypertension. In hypertension the minute-volume output of the heart is not much changed, but the weight of the heart becomes greatly increased as a rule, whereas in hyperthyroidism the minute-volume output of the heart is greatly increased but the weight of the heart is relatively little changed. Apparently obstruction to blood flow is a much greater strain than increase in minute-volume output with lessened resistance to blood flow.

The question of malnutrition as a factor in the size of the heart is very important, as had been shown by a number of men in experimental work with animals. When the nutrition of animals maintained in a state of chronic hyperthyroidism is kept normal, the heart gains moderately in weight, sometimes as much as 50 per cent over the normal limit. If, however, malnutrition sets in, the weight that the heart has gained is rapidly lost, and when malnutrition is severe, a small, atrophic heart may result.

Dr. T. R. Harrison, Nashville, Tenn.—The relatively slight degree of cardiac hypertrophy in these cases is of great interest. Probably it is related to the fact that the work of the heart per beat is not much increased in patients with thyrotoxicosis. Other types of cardiac disorder are likely to be associated with increased work per beat as well as increased work per minute. It is likely that hypertrophy is dependent on the work per beat rather than on the work per minute.

Dr. Harold E. B. Pardee, New York, N. Y.—I should like to ask Dr. Kepler how many cases of heart failure there were without auricular fibrillation being present and the approximate age of those patients.

Dr. E. J. Kepler, Rochester, Minn.—Regarding Dr. Fahr's question I may say that the weight of the heart was greater than the weight calculated from the standard in about one-half the cases, if the usual weight of the patient was used in making the calculation. If the last recorded weight of the patient, which closely approximates the actual weight of the body at the time of death, was used, it was found that in nearly every instance the weight of the heart exceeded the standard. Furthermore, we used as a standard the figures which Smith gave as the maximal normal weight of the human heart. In other words, we selected the most rigid standard available and found that in one-half the cases the weight of the heart exceeded the standard.

It is important to bear in mind, however, that, strictly speaking, we are discussing in this paper a disturbance in the ratio of heart weight to body weight; and we assume that if this ratio is increased, there has been a "morbid enlargement or overgrowth" of the heart, or, in other words, hypertrophy. At the present time we have no reason to believe that such an assumption is incorrect.

Dr. Pardee, I believe, raised the question of the frequency of auricular fibrillation with congestive heart failure. Practically all of the patients who had congestive heart failure had auricular fibrillation or auricular flutter.

The question also has been raised regarding the part which age plays in the production of congestive heart failure in hyperthyroidism. It is well recognized, clinically, that congestive heart failure in hyperthyroidism is a phenomenon encountered rarely in young patients and comparatively frequently in middle-aged and elderly patients. Consideration of our data does not, however, enable one to formulate an opinion regarding the influence which age has in the production of congestive failure because the cases are distributed unevenly through the various decades. The relationship of age to congestive heart failure can be studied best from clinical data. Our data do show, we believe, that congestive failure may occur in hyperthyroidism in the absence of any independent cardiac disease, and purely as the result of hyperthyroidism, plus the physiological diminution of cardiac reserve incidental to advancing years.

Discussion of paper of Drs. Morris W. Lev and Walter W. Hamburger. (See p. 109.)

Dr. George Fahr, Minneapolis, Minn.—I should like to ask Dr. Lev something about the diastolic pressures in these cases. I have always been surprised that we do not have more angina pectoris in severe exophthalmic goiter than we do. From determinations of minute-volume we know that in the cases described here the minute-volume will be at least double. The heart is not as efficient a machine against increased minute-volume as it is against pressure, so that when the minute-volume has doubled, the heart is requiring a consumption of oxygen more than double the normal.

Practically all the flow through the coronaries takes place during diastole. The diastolic time is cut down because these hearts are rapid. As we all know, the majority of cases of hyperthyroidism do show a lower diastolic pressure. If only a little coronary disease is present then, all you need to do is to lower your diastolic pressure a little bit and you can expect to have angina. It would be very interesting if we could find out in these cases of angina pectoris whether the diastolic blood pressure had been lowered, say down to 50 or some value like that, such as we once in a while find in the clinic.

Dr. Louis F. Bishop, Jr., New York, N. Y.—I should like to ask Dr. Lev what the electrocardiographic findings were in this series of cases of angina associated with hyperthyroidism. I should also like to ask if fibrillation was present in any of the cases with pain or whether there were any examples of paroxysmal tachycardia.

Dr. Morris W. Lev, Chicago, Ill.—In answer to Dr. Fahr, the diastolic pressures of all of our patients were normal or increased. We did not have any unusually low diastolic readings. If anything, they tended to be above the usual rate.

In answer to the question regarding the electrocardiographic pictures, in this particular series we took special pains to exclude those patients who might be accused of being frank coronary cases, or of having any other cardiac disturbance judging from the electrocardiographic pictures.

None of our patients, as I recall, had any auricular fibrillation or paroxysmal tachycardia. Anything that might have suggested that the patient was suffering from something other than angina would have excluded that case from our series.

Discussion of paper of Drs. Johnson McGuire and Margaret Foulger. (See p. 114.)

Dr. Harold E. B. Pardee, New York, N. Y.—Will Dr. McGuire explain what he means by "rolling contour of the T-wave"? Also did he obtain more than one lead of these dogs? If not, it is hard to see how the observations can be final, because the lack of variation in one lead is not an indication that the other leads are also unchanged.

Dr. Johnson McGuire, Cincinnati, O.—In regard to the definition of "rolling contour," I am very much interested to know if anyone can tell where that expression originated. It didn't with me. When I reviewed the literature, I found the expression rather often. To me it simply means that the summit of the wave is broad and not peaked. In normal young people with "T" waves of high voltage the wave rises sharply to a relatively sharp summit. In our examples the apex of the wave was smooth and sloping. I shall add a diagram to my paper to illustrate this difference.

In regard to the question about leads, I think nowhere have I found any description of changes occurring in thyrotoxicosis except in Lead 2, and in our dogs Lead 2 was used. I think it is an interesting suggestion that other leads should be examined, especially as in one or two of the cases which I showed, following the administration of thyroid extract, important changes occurred in Lead 1.

Discussion of paper of Dr. Lewis M. Hurxthal.

Dr. E. J. Kepler, Rochester, Minn.—What was the frequency with which demonstrable enlargement of the heart took place and was followed by a diminution in size?

Dr. Bayard Holmes, Chicago, Ill.—Has Dr. Hurxthal compared the effects of digitalis alone and Lugol's solution alone in regard to their ability to produce improvement of the cardiac dilatation before operation? My experience personally has been that digitalis alone has had comparatively little effect while Lugol's alone had the result that he has demonstrated here.

Dr. Lewis M. Hurxthal, Boston, Mass.—About the frequency of dilatation, there were eighty cases without congestive heart failure. Of those eighty, nineteen showed definite changes as shown by superimposition of films. Eight of those were larger, seven were unquestionably larger, and four were smaller. Of the cases which showed larger hearts after operation, there were one or two with postoperative myxedema. Some had definite hypertensive disease and in one or two we felt that it could readily be concluded that the increase or gain of weight had something to do with it. We had one boy with severe exophthalmic goiter who weighed ninety pounds before operation and one hundred and fifty pounds after operation. He had gained two-thirds of his body weight. Although the diaphragm was higher after operation in his case, nevertheless we felt that the heart shadow was definitely larger.

In all cases with congestive heart failure there was a definite reduction in the size of the heart. In twenty-five cases of auricular fibrillation, definite reduction in the size of the heart took place in fifteen. In other words, congestive failure, not auricular fibrillation, is probably the thing which causes the dilatation. We have been able to check cases of nonthyroid heart disorders with congestive heart failure and we have been able to demonstrate the same thing, but not so conclusively because there is usually fluid in the chest, making comparisons difficult.

About the use of digitalis and Lugol's solution, I do not believe any rule can be laid down. We have purposely withheld Lugol's solution in patients with auricular fibrillation and have given them digitalis and had excellent results; that is, a relief of congestive heart failure and a certain amount of slowing of the pulse. We have also withheld digitalis in some cases and given Lugol's and obtained good results. In other cases where Lugol's solution had been given and edema had increased, digitalis cleared all signs of congestive heart failure. Of course, knowing one will work in some cases and the other will work in other cases, we give them both together in this type of case as soon as the patient enters the hospital.

Discussion of paper of Drs. Paul S. Barker, Anne L. Bohning, and Frank N. Wilson. (See p. 121.)

Dr. G. Werley, El Paso, Tex.—I noticed, if I understood, that the mortality of operation in fibrillation cases was 20 per cent. I do not understand whether these cases were operated upon during the fibrillation or after the heart had been corrected by digitalis and iodine. I want to bring up our little experience in El Paso.

It seems to me that a much safer method of handling those cases would be to use x-ray and radium, because in our small series of cases we have had no mortality at all. The patients as a rule have not been put to bed. They have not been prepared in any way, and the results have been perfectly good. The treatment is prolonged, but I cannot see any difference between the end-results in these cases and in the cases that were operated.

Dr. George Fahr, Minneapolis, Minn.—I understood you to say, Dr. Barker, that there were signs of toxic effect before there was an increase in the work of the heart. That seems very strange to me, and I should like to ask how you measured the work of the heart.

Dr. Lewis M. Hurxthal, Boston, Mass.—I should like to discuss a few points which bear on the question of thyrotoxicosis damaging the heart. In the first place, dis-

turbances of conduction; i. e., various types of heart-block, are rare in hyperthyroidism. When present, they can usually be ascribed to other things. Another thing that we must not forget is that there is apparently a reversible change. After relief of hyperthyroidism, the heart muscle, from the functional standpoint, seems just as good as before the onset of hyperthyroidism, excluding the possibility of established fibrillation. It seems to me therefore that there is not much evidence of damage to the heart itself from thyroid toxicity.

Dr. E. J. Kepler, Rochester, Minn.—The mortality rate of hyperthyroidism associated with auricular fibrillation seems to be unduly high in the series of cases presented. It occurs to me that the energetic treatment of these patients with digitalis may be a factor in part responsible for this. I am of the opinion that digitalis should be used with caution in treating hyperthyroidism. At the present time digitalis in the treatment of congestive failure associated with hyperthyroidism is used comparatively rarely at the Mayo Clinic. Treatment with ammonium nitrate and salyrgan usually results in prompt diuresis and compensation is restored without the use of digitalis. When overtreatment with digitalis is used, undesirable toxic effects may appear before the pulse rate or cardiac decompensation is affected.

Dr. Lewis M. Hurxthal, Boston, Mass.—We are using digitalis routinely in all cases of auricular fibrillation except in cases of fibrillation without congestive heart failure, in which the rate does not average more than 100 per minute. The mortality at the Clinic up to 1928 on the 143 cases of thyrocardiacs with congestive heart failure or auricular fibrillation was only three per cent. The mortality since that time in the general run of cases is around one per cent. I think that is about the same percentage of mortality that is found in any thyroid clinic.

Personally, I have never seen any harmful effects from using digitalis in individuals with hyperthyroidism.

Dr. Harold E. B. Pardee, New York, N. Y.—I should like to ask about the excretion rate of digitalis in these patients. It has seemed to me, although I have made no statistical study, that patients with hyperthyroidism need more digitalis than the ordinary patient. I have followed two patients whose metabolism was varying from time to time. As the metabolic rate would go up, the need for digitalis would increase.

I should also like to know in connection with this mortality rate if the patients who died were under what you would consider proper digitalis control at the time of operation or if they were culled from the days before proper digitalis control was understood.

Dr. Paul S. Barker, Ann Arbor, Mich.—I shall try to answer some of the questions. Several of our patients were given quinidine prior to operation and somewhat over half of them returned to normal rhythm, but in all of these the fibrillation returned.

I admit that the mortality in these cases seems high. You have no doubt noticed that the age of these patients with fibrillation is considerably above the average age of patients with toxic goiter. Many of them were in poor condition and were not operated upon for this reason. The mortality was very high in this group. An effort was then made to see what could be done by means of thyroidectomy in similar cases. It is my belief that the results are better with thyroidectomy than without it, excepting in the very aged and those in extremely critical condition. Since the time at which these cases were treated, of course our ability to treat such cases has improved, and our mortality is much lower now, partly because of improved management in the postoperative period.

Regarding the work of the heart in the two cases that I cited, between attacks they were apparently perfectly normal people, with normal heart rate and normal blood pressure, and this is evidence that the work of the heart was not increased.

They did not have arteriosclerosis. The work of the heart, however, was not actually determined in these patients. I have estimated the work of the heart in other patients, and also in the cases of Davies, Meakins, and Sands,* in which the necessary data were given in connection with studies of the blood flow. The work of the heart was estimated according to the method described by Dr. Fahr,** and it is increased in fully developed Graves' disease.

We have not seen harmful effects from digitalis. We have seen beneficial effects in some patients. In others, however, we have given full doses without any beneficial effects that we could determine. I do not know why digitalis is less effective in hyperthyroidism unless perhaps it is utilized, eliminated, or destroyed more rapidly, or because vagus tone is low. It is well known that patients with toxic goiter require much larger doses of morphine and also that they tolerate larger doses of quinine than the average patient, and no doubt experience will show that they tolerate other drugs in larger amounts.

It is my impression, although I do not have the figures, that the rate of excretion of digitalis is increased in hyperthyroidism. The manner of administering digitalis in this group of cases was such that we had to take into account not only the tolerance to a single large dose, but also the excretion rate, and it seems that both are increased in these patients.

Discussion of paper of Dr. John P. Anderson. (See p. 128.)

Dr. William D. Reid, Boston, Mass.—What was the maximum and average amount of quinidine given to these patients?

Dr. John P. Anderson, Cleveland, O.—I am sorry that I did not prepare any statistical record of the amount used. I would say that the average patient received about six doses or a total of thirty grains. Sometimes one or two doses prove sufficient, but it is not at all infrequent for patients to require the second and third day's course of quinidine therapy and a few required the full four days' course. One such patient still had an abnormal rhythm on the fourth day, and I ordered the quinidine to be stopped at midnight. A normal rhythm was established about two o'clock that morning.

Discussion of paper of Drs. Morris W. Lev and Walter W. Hamburger. (See p. 134.)

Dr. Harold E. B. Pardee, New York, N. Y.—I should like to ask whether the patients were at rest before the control electrocardiogram was taken.

Dr. Morris W. Lev, Chicago, Ill.—The taking of electrocardiograms was no novelty to them. They had had electrocardiograms taken previously for routine work, and there was no mental effect or any particular excitement. As a matter of fact, they were at rest at least fifteen minutes before anything was done.

*Davies, H. W., Meakins, J., and Sands, J.: Heart **11**: 299, 1924.
Fahr, George: Proc. Soc. Exper. Biol. & Med. **24: 405, 1927.